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Original Contribution

Adverse events associated with ketamine for procedural sedation in adults

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Abstract

Study Objectives: Ketamine is widely used as a procedural sedation agent in pediatrics, where its safety and efficacy are supported by numerous studies. Emergency physicians use ketamine infrequently in adults, as it is believed to have a more significant side effect profile in this population. However, adult data on ketamine use in the emergency medicine literature are sparse. Our objective was to determine ketamine's adverse effect profile in adults when used for procedural sedation.

Methods: We performed a literature review based on adverse effect research methodology recommendations. PubMed, EMBASE, TOXNET, and a variety of specialized databases were queried without regard to publication date or language. Experts were contacted to locate additional data. Inclusion criteria included adult study; ketamine used to facilitate the performance of painful procedures; dose of at least 1 mg/kg intravenous or at least 2 mg/kg intramuscular; original data and adverse events reported; spontaneously breathing patient, and no continuous cotherapies. Studies that met inclusion criteria were abstracted onto structured forms and their results qualitatively summarized.

Results: Of the 5512 unique citations that were evaluated, 87 met criteria for inclusion. Most studies were performed in the 1970s and published in the anesthesia literature. Contexts, end points, and methodological quality varied widely across studies. Ketamine reliably produces conditions that facilitate the performance of painful procedures. Pharyngeal reflexes are generally preserved and cardiovascular tone stimulated, including a rise in blood pressure and myocardial oxygen demand. Laryngospasm and airway obstruction are reported, and though ketamine is a respiratory stimulant, a brief period of apnea around the time of injection is common. Reports of significant cardiorespiratory adverse events are rare, despite ketamine's frequent use in austere, poorly monitored settings. Dysphoric emergence phenomena occur in 10% to 20% of cases; sedating medications are effective in preventing and managing these reactions.

Conclusion: When ketamine is used for procedural sedation in adults, emergence phenomena occur in 10% to 20% of patients. Although providers must be prepared to recognize and manage airway obstruction, cardiorespiratory adverse events are rare and typically do not affect outcomes.

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1. Introduction

Ketamine hydrochloride is a dissociative agent that was first used in humans in 1965 [1]. It is a phencyclidine derivative developed when the potential was appreciated for this class of compounds to produce a state resembling general anesthesia without cardiorespiratory depression at therapeutic doses. When given by the intravenous or intramuscular route, ketamine rapidly causes profound analgesia, amnesia, and sedation as the patient breathes spontaneously, and blood pressure, heart rate, and protective airway reflexes are maintained or stimulated [2]. These features, combined with low cost and a large therapeutic window [3], have made ketamine the anesthetic of choice in resource-poor or austere environments, where monitoring equipment may be rudimentary or absent and a single operator provides the anesthetic, monitors the patient, and performs the procedure [4]. In western emergency medical practice, ketamine is frequently used to facilitate painful procedures in children and has proven safe and effective in numerous studies [5-18]. In adults, however, it is commonly believed that ketamine's adverse effect profile—most importantly so-called emergence reactions—favors the use of other agents [19].

Ketamine is accepted as a standard agent of pediatric procedural sedation [20]. However, usage studies, which are not experimental but report on the current practice of an institution or set of institutions, show that it is used infrequently in emergency departments (EDs) that treat both adults and children [21-23].

Furthermore, a recently published registry showed that of all agents typically administered for procedural sedation, ketamine was associated with the fewest adverse events yet used the least often in this setting [23]. In a review of 979 consecutive procedural sedation cases at an adult tertiary care center, ketamine was used in 2.7% [24], and a survey of community ED directors showed that ketamine is unavailable in 41% of departments [25]. A total of 3 trials evaluating ketamine for procedural sedation in adult patients have been published in the emergency medicine literature [26-28]. We therefore undertook to review all available literature with the objective of determining ketamine's adverse effect profile in adults when used for procedural sedation.

2. Methods

A search strategy was developed after a consideration of adverse effect research methodology reviews [29-31] and in accordance with criteria outlined in the adverse effects appendix to The Cochrane handbook [32].

1. All abstracts fulfilling the following PubMed search string were reviewed (PubMed ketamine adverse effects heading and specific effects search).

> ["ketamine/adverse effects"[Mesh Terms] OR "ketamine/ poisoning"[Mesh Terms] OR "ketamine/toxicity"[Mesh Terms] OR "ketamine/ contraindications"[Mesh Terms] AND "humans"[MeSH Terms]] OR [(("ketamine"[MeSH Terms] OR Ketamine[Text Word]) AND (adverse[All Fields] OR side[All Fields] OR (("psychomotor agitation" [TIAB] NOT Medline[SB]) OR "psychomotor agitation" [MeSH Terms] OR agitation[Text Word]) OR psychological[All Fields] OR (("laryngismus"[TIAB] NOT Medline [SB]) OR "laryngismus"[MeSH Terms] OR laryngospasm [Text Word]) OR (("bodily secretions"[TIAB] NOT Medline[SB]) OR "bodily secretions"[MeSH Terms] OR secretions[Text Word]))) NOT ("ketamine/adverse effects"[Mesh Terms] OR "ketamine/ poisoning"[Mesh Terms] OR "ketamine/toxicity"[Mesh Terms] OR "ketamine/contraindications"[Mesh Terms] AND "humans"[MeSH Terms]) AND "humans"[MeSH Terms]]

2. All summaries not fulfilling the prior PubMed search string but fulfilling the following PubMed search string were reviewed (PubMed ketamine text search).

> ("ketamine"[MeSH Terms] OR ketamine[Text Word])

3. All summaries fulfilling the following EMBASE search string were reviewed (EMBASE adverse effects and drug therapy search).

> exp KETAMINE/ae, dt

4. All summaries fulfilling the following TOXNET search string were reviewed (TOXNET ketamine title search). This included TOXLINE and 9 associated databases.

> ketamine [title]

5. The following databases were manually searched for relevant citations: The Cochrane Library; The Australian Adverse Drug Reactions Bulletin; The European Public Assessment Reports from the European Medicines Evaluation Agency; MedWatch, The FDA Safety Information and Adverse Events Reporting Program; and UK Current Problems in Pharmacovigilance.

6. Selected textbooks in the fields of emergency medicine, anesthesiology, and clinical pharmacology were reviewed and mined for references [33-43].

7. Selected review articles in the emergency medicine, anesthesiology, and clinical pharmacology literature were mined for references [2,19,44-59].

8. Selected experts in the field were petitioned for obscure or unpublished data.

9. The bibliographies of all included studies were mined for references.

The literature search was executed in May 2006 and all articles produced were evaluated by a single reviewer. Each citation was marked for retrieval or put in 1 of 7 exclusion categories as follows:

i. Not ketamine. Articles that did not study ketamine were excluded.
ii. Not a human adult study. Animal studies and pediatric studies were excluded. A *pediatric study* was defined

as one in which more than half of study patients were younger than 18 years. Several articles divided results into adult and pediatric sections; the adult data from these articles were included.

iii. Low dose. Only trials that studied ketamine in doses of at least 1 mg/kg intravenously administered in a 30-minute period or 2 mg/kg intramuscularly administered in a 30-minute period were included.

iv. No adverse events. Only studies that reported either psychiatric or cardiorespiratory adverse events were included. A *cardiorespiratory adverse event* was defined as a change in patient condition that required bag-valve-mask (BVM) ventilation, invasive airway management, or specific measures to correct alterations in blood pressure, heart rate, or heart rhythm. A *psychiatric adverse event* was defined as any indication of fear, agitation, or psychologic distress in the recovery period; these were variously described as hallucinations, unpleasant dreams, and motor restlessness among many other terms. The rate of patient satisfaction with anesthesia was allowed as a surrogate for psychiatric adverse event reporting when applicable.

v. Inappropriate use for the purposes of this study. The following types of studies were excluded: trials that studied patients who were endotracheally intubated; trials that used continuous cotherapies such as a diazepam drip or an inhalational anesthetic (preparatory cotherapies or premedicants, such as diazepam given preinduction, were allowed); trials that studied ketamine for a purpose other than facilitating painful procedures (eg, asthma, perioperative pain, chronic pain); trials that used supplemental conduction anesthesia (eg, nerve blocks, epidural, or spinal anesthesia); trials that did not study racemic ketamine;

Ketamine QSR Abstraction Form

1. Inclusion and exclusion criteria:

   a. Are more than 50% of patients in the study presumably adults? If no, stop.

   b. Did the investigators use ketamine in a dose greater than 1 mg/kg IV or 2 mg/kg IM within a 30 minute period? If no, stop.

   c. Does the paper report either psychiatric adverse events (e.g. dysphoria, agitation, nightmares, hallucinations, unpleasant dreams, or other such phenomena associated with emergence from ketamine anesthesia) or cardiorespiratory adverse events (e.g. need for BVM ventilation, airway support, intubation, lowering or raising of heart rate or blood pressure)? If no, stop.

   d. Did the paper study patients who breathed spontaneously throughout the procedure? Studies of intubated patients are not allowed. If no, stop.

   e. Did the patients receive a continuous cotherapy in addition to ketamine, such as a diazepam/propofol *drip*, or an inhalational agent such as nitrous oxide or volatile anesthetic? No continuous cotherapies are allowed. If yes, stop.

   f. Is ketamine being used to facilitate a painful procedure? Studies of ketamine for some other purpose, such as asthma, perioperative pain, and chronic pain are not allowed. If no, stop.

   g. Does the paper report original data? Review articles are not allowed. If no, stop.

If the paper satisfies all these criteria, it is likely suitable for inclusion. Next is the abstraction. Many papers will not completely answer these questions, if you can not determine the full answer to the question from the paper, indicate this.

2. How many patients and what sort of patients were included? For example, does the paper report on burn patients, patients undergoing gynecologic instrumentation, minor surgery, or painful procedures in the emergency department?

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3. What sort of paper is it? Is it an experimental trial, with a control group? Is it a case report? A historical description? Summarize the setup of the study, including details of what patients in each study group received, if there is more than one group.

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4. How much ketamine was given, and by what route? For example, 2 mg/kg IV over 60 seconds. If supplemental doses were given for longer procedures, indicate this.

Fig. 1 Abstraction Form.

5. Were other medications given? If so, list them and when they were given relative to the ketamine.

6. What was the setting, and who performed the anesthesia? For example, an anesthesiologist in an operating room, a surgeon in a rural hospital, or an emergency physician in an emergency department?

7. Adverse event reporting methodology:

a. What kind of cardiorespiratory monitoring was performed? Did the authors indicate that they were looking for cardiorespiratory adverse events prospectively?

b. What kind of psychiatric adverse event monitoring was performed? Did the authors indicate that they were looking for psychiatric adverse events prospectively?

c. Were the authors looking for any other sort of adverse events as part of their study design?

8. Adverse events results:

a. What was the incidence of cardiorespiratory adverse events? If the paper states that there were none, indicate that. If the paper says something more vague, such as "no complications," indicate that.

b. What was the incidence of psychiatric adverse events? What was the nature of these events? If reported, qualify the events as severe or mild, and whether further treatment (with a sedative) was used.

c. Were any other adverse events (e.g. vomiting, hypertonus, rash) reported? If so, indicate their incidence.

9. Possible confounders: If the study reports limitations, summarize them. If you identify any confounding issues, report them.

Fig. 1 (*continued*).

volunteer studies; trials that studied ketamine for recreational use or for Rapid sequence intubation (RSI); and intranasal, regional, subcutaneous, intrathecal, subarachnoid, epidural, transdermal, intraarticular, jet injection, patient-controlled analgesia (PCA), lollipop, mouthwash, intraperitoneal, transmucosal, or rectal ketamine studies.

vi. No abstract. Articles without an abstract available in the referring database were excluded unless the title clearly suggested appropriateness. Foreign language articles without an abstract were excluded.

vii. No original data. Articles that did not report original data were excluded, unless selected as a review article to be mined for references.

All articles not marked with an exclusion criterion were retrieved and their full text reviewed. Studies that then fell into an exclusion category on closer inspection were marked as "Reviewed/not abstracted." The remainder of the studies were abstracted onto structured forms (Fig. 1) that constitute the results of the present study. The adequacy of anesthesia, the use of antisialogogues, and the cardiostimulatory effect of ketamine were not abstracted unless of particular interest, as these elements showed little variation across studies.

Given the heterogeneity in design and quality of the component studies, no attempt was made to combine data and no statistical analyses performed. Results are summarized by qualitative analysis.

3. Results

The search strategy produced 5512 citations, of which 223 met inclusion criteria for retrieval. Of these, 87 met criteria for inclusion after close inspection and were abstracted [4,23,24,26-28,60-138]. Four articles published in a language other than English are included in the results [137-140]. Non-English language articles in Spanish, German, Portuguese, Russian, and French were evaluated; other non-English language articles were excluded.

Results are presented in Table 1.

4. Analysis/narrative summary

Of 83 studies applicable to emergency medicine, 36 reported on 100 or more patients; of these, 10 reported on 500 or more patients. Most experimental trials were performed in the 1970s and published in the anesthesia literature; these studies are of variable methodological quality and use a wide variety of comedications, many of which are not available in modern EDs.

This sample of studies indicates that ketamine is dependable in its *efficacy*. In dissociative doses, ketamine reliably produces analgesia. Several studies report that in patients who receive ketamine regularly (eg, for burn-related procedures), tolerance does develop, and the dose must be increased [116,128].

Ketamine demonstrates a high degree of *safety*. In more than 70 000 patients described in this review, a single adverse cardiorespiratory event of lasting significance in an adult is attributed to the drug—a case report describing "Hypoxic cardiac arrest secondary to respiratory depression...in a debilitated adult [91]." No further circumstances or details are provided.

Despite work demonstrating radiologic evidence of contrast aspiration under ketamine anesthesia [99], there are no reported cases of clinically detected aspiration associated with ketamine. Fully dissociated patients maintain their *pharyngeal reflexes* and will swallow a liquid if challenged [99]. Many articles report, however, on patients who required airway maneuvers such as a chin-lift or jaw-thrust for positional obstruction [26,66,67,104,106]. *Laryngospasm*, a rare [10] complication in children, is reported even less frequently in the larger adult airway and is either transient or responsive to BVM ventilation [4,27]. The specter of laryngospasm is often cited to contraindicate ketamine for procedures involving the posterior oropharynx, though studies describing its use for endoscopic; ear, nose, and throat; and dental procedures suggest that it may be safe in this context [46,131,134].

Ketamine is a respiratory stimulant [141] but produces transient *respiratory depression*, which may include apnea, usually within the first 2 to 3 minutes of administration [76,81,87,90,110]. This effect appears to be more likely if ketamine is delivered rapidly by the intravenous route but when used as monotherapy is rarely, if ever, of clinical significance. Respiratory depression requiring BVM ventilation does occur when agents known to depress respiration, such as those in the benzodiazepine class, are given concurrently [27,28,66,129].

A transient mild increase in heart rate and significant increase in systolic and diastolic blood pressure almost always accompany ketamine administration [142,143]. These cardiostimulatory effects can be mitigated by sympatholytic agents [61,108,139,144].

Psychiatric adverse events are reported in 0% to 76% of patients emerging from ketamine anesthesia. Unfortunately, end points of clinical significance (dysphoria, patient satisfaction) were often not studied and frequently markers of uncertain consequence (dreams, hallucinations, delirium) used as a surrogate.

In those studies of ketamine monotherapy where patient-oriented outcomes are assessed, the rate of psychiatric adverse events is 10% to 20% [61,79,92,93,100,101,115]. Sedating agents are highly effective at both preventing and terminating ketamine *emergence reactions* [27,61,68,70,71,74,79,93,97,101,108,114,115], and environmental interventions such as preinduction counseling and the provision of music are also successful in reducing the occurrence of these events [73,75,116,145].

The incidence of *vomiting* varied widely across studies but can be expected in 5% to 15% of patients [27,67,78,100,106,115]. These episodes generally occur after the patient has emerged from a dissociative state.

An evanescent patchy erythematous *rash* about the upper torso occurs in 5% to 20% of patients shortly after ketamine injection and disappears within 20 minutes. It requires no treatment and does not recur with further ketamine administrations [101,119,120,128].

Ketamine commonly causes *purposeless movements* [100] and infrequently causes *hypertonus* that on occasion can interfere with the procedure it was given to facilitate [94,146].

Anticholinergic medications are routinely given to children to prevent *hypersalivation*; this occurs less frequently in adults and is rarely of clinical significance, though most studies included an antisialogogue in their comedication regimen.

5. Discussion

The ideal agent for facilitating painful procedures in the ED would be reliably effective as an analgesic, anesthetic, amnestic, and anxiolytic with a wide therapeutic index across the spectrum of patients, conditions, and routes of administration; cause a rapid, titratable, and reversible response with a short duration of action; preserve protective reflexes and cardiorespiratory tone; and be free of adverse effects.

Table 1 Results

	A	B	C	D	E	F
1	Citation no.	Citation	Study design	Adverse event reporting methodology	Results	Possible confounders
2	86	Abajian JC, Page P, Morgan M. Effects of droperidol and nitrazepam on emergence reactions following ketamine anesthesia. Anesth Analg 52:3, 385-9(1973) eng.	60 patients undergoing minor surgical procedures received per orem (oral) droperidol, 20 mg, and PO nitrazepam, 10 mg, followed 60-90 min later by intravenous ketamine 2-2.2 mg/kg given for 45-60 s. Supplementary half doses were given as needed during the procedure.	Cardiorespiratory status was continuously monitored. Psychiatric adverse events were prospectively sought.	"Respiratory obstruction necessitating intervention on the part of the anesthesiologist" occurred in 12% of patients. Seventeen percent of patients reported having unpleasant dreams and 10% of patients reported having terrifying dreams. Eighteen percent of patients reported the anesthetic unacceptable.	PO premedicants unlikely to be used in modern emergency practice.
3	121	Abu Khalaf A, Takrouri M, Toukan A, Abu Khalaf M, Amr S. Ketamine hydrochloride as sole anesthetic for open liver biopsy. Middle East J Anaesthesiol 9:6, 537-43(1988) eng.	12 patients undergoing open liver biopsy received IV ketamine 2 mg/kg for 60 s, followed by supplementary doses of 0.75 mg/kg as needed.	Cardiorespiratory status was continuously monitored. No psychiatric adverse event reporting methodology is presented. Liver function was prospectively followed postoperatively.	No cardiorespiratory adverse events occurred. Of 12 patients, 2 had unpleasant dreams; 3 patients in this cohort required intraoperative muscle relaxation and endotracheal intubation for "respiratory tagging" that limited surgical maneuvers.	
4	135	Adesunkanmi AR. Where there is no anaesthetist: a study of 282 consecutive patients using intravenous, spinal and local infiltration anaesthetic techniques. Trop Doct 27:2, 79-82(1997) eng.	Retrospective review of 203 patients undergoing a variety of surgical procedures at 2 Nigerian medical centers. Anesthesia was conducted by the surgeon. Patients received IV diazepam, 10 mg, (adults) or 0.15 mg/kg (children) followed by IV ketamine, 2 mg/kg, (adults) or IM ketamine, 5 mg/kg. Incremental smaller doses were given IV intraoperatively as needed.	Cardiorespiratory status was continuously monitored. No psychiatric adverse event reporting methodology is presented.	7 deaths occurred, none attributable to the anesthesia. No cardiorespiratory adverse events were reported. Emergence delirium/confusion was reported in 56.7% of patients, with dreaming reported in 5.4% of patients.	Dysphoria and patient acceptance not distinguished from emergence reactions.

5	127	Ashraf Ganatra M, Bhatti BT, Durrani KM. Ketamine in burn wound management. Specialist 11:4, 327-33(1995) eng.	32 patients undergoing surgical procedures in a Pakistani hospital burn unit received IV ketamine, 2 mg/kg, with supplementary 1 mg/kg doses as needed. For further procedures, patients received ketamine on postoperative days no. 2, 4, and 6 while no ketamine was used on days no. 1, 3, and 5.	Cardiorespiratory adverse event reporting methodology is not presented, though hemodynamic measurements are reported in the results. "Behavior during recovery" was prospectively measured.	2 patients died of burn-related complications. No cardiorespiratory adverse events are reported. Hallucinations were noted in 6/32 cases and "nightmares and anxiety" occurred in 2/32 cases. Of 27 patients available for final evaluation, all 27 preferred to receive ketamine to facilitate painful procedures (the alternative appears to have been no anesthesia).	Results are difficult to interpret. Three patients left against medical advice before all planned procedures were performed.
6	130	Awojobi OA. Ketamine anaesthesia for caesarean section. Trop Doct 14:4, 165(1984) eng.	Brief historical account of 35 patients undergoing emergency. cesarean delivery and 1 patient undergoing cesarean scar revision in a Nigerian district hospital. Patients received IV chlorpromazine, 50 mg, or IV diazepam, 10 mg, 15 min before induction with IM ketamine, 250 mg. No further doses of ketamine were given; generous local anesthesia was used in this technique.	No adverse event reporting methodology is presented.	No adverse events are reported in this account.	Descriptive review.
7	108	Ayim EN, Makatia FX. The effects of diazepam on ketamine anaesthesia. East Afr Med J 53:7, 377-82(1976) eng.	105 patients undergoing curettage for incomplete abortion received IV ketamine, 1-2 mg/kg, and were randomized to one of 3 groups. Group 1 received ketamine alone; group 2 received IV	Cardiorespiratory status was continuously monitored. Psychiatric adverse events were prospectively sought.	No cardiorespiratory adverse events occurred. Incidence of "highly unpleasant reactions," which included shouting, restlessness, crying, and terrifying dreams, was 32% in group 1,	Patient acceptance not assessed. Psychologically traumatic procedure.

(continued on next page)

Table 1 (*continued*)

	A	B	C	D	E	F
			diazepam, 10 mg, 5 min preinduction; group 3 received IV diazepam, 10 mg, at the end of the procedure, as the patient showed signs of recovering.		11% in group 2, and 8% in group 3. Patients in group 2 were noted to have a significantly lower incidence of poor anesthesia, as well as a significant attenuation of the rise in blood pressure and heart rate seen in groups 1 and 3.	
8	85	Azar I, Ozomek E. The use of ketamine for abdominal tubal ligation. Anesth Analg 52:1, 39-42(1973) eng.	50 patients undergoing postpartum tubal ligation received IV meperidine, 50 mg, followed 15-30 min later by IV ketamine, slowly infused until adequate anesthesia was obtained. Repeat boluses of 20 mg ketamine were given prn (as needed).	Blood pressure, heart rate, minute ventilation, arterial blood gas measurements, and postoperative side effects were prospectively sought.	Average induction dose was 1.27 mg/kg. No reported respiratory or cardiovascular adverse events. 27% of patients had "incoherence or hallucinations;" of these, 3 patients had "vivid hallucinations."	No control group. Dysphoria and patient acceptance not distinguished from hallucinations and incoherence.
9	93	Becsey L, Malamed S, Radnay P, Foldes FF. Reduction of the psychotomimetic and circulatory side-effects of ketamine by droperidol. Anesthesiology 37:5, 536-42(1972) eng.	214 patients undergoing elective termination of pregnancy were randomized in double-blind fashion to receive a preinduction or preemergence regimen or placebo. All patients received IV ketamine 2.5 mg/kg given for 30 s. Preinduction regimens included droperidol 75 μg/kg and droperidol, 75 μg/kg, with fentanyl 0.375 μg/kg. Preemergence regimens included diazepam, 150 μg/kg, and thiopental, 1.5 mg/kg. All drugs were given intravenously.	Cardiorespiratory parameters were prospectively measured and recorded. Psychiatric adverse events were prospectively sought in standardized fashion.	No cardiorespiratory adverse events occurred. Rates of restlessness, crying, and screaming, as well as the characterization of "agitated" or "frightened" were between 10% and 20% in placebo patients. These adverse psychiatric events were not diminished in the diazepam or thiopental group, but were reduced to less than 5% in the droperidol and droperidol/ fentanyl groups. The addition of fentanyl to droperidol did not confer an appreciable benefit. Postoperative vomiting was common in all groups; this was attributed to the uterotonic medications given as part of the abortive procedure.	

10 [111]	Bishop RA, Litch JA, Stanton JM. Ketamine anesthesia at high altitude. High Alt Med Biol 1:2, 111-4(2000) eng.	11 patients undergoing minor procedures by general practitioners in a hospital in the Mt Everest region of Nepal, altitude 3900 m, received IV midazolam, 0.05 mg/kg, followed by IV ketamine, 1 mg/kg, given for 1-2 min, with smaller supplemental doses as needed.	Cardiorespiratory status was continuously monitored. No psychiatric adverse event reporting methodology is presented.	No cardiovascular adverse events occurred. Of 11 patients, 3 required supplemental oxygen for saturation <80% more than 60 s unresponsive to basic airway maneuvers. Of these three, 2 were unacclimatized to the altitude. No "emergent nightmares" occurred.	Altitude.
11 [113]	Bonanno FG. Ketamine in war/tropical surgery (a final tribute to the racemic mixture). Injury 33:4, 323-7(2002) eng.	62 patients undergoing a variety of surgical procedures received IV ketamine, 2 mg/kg, (n = 60) or IM ketamine, 4-5 mg/kg, (n = 2), followed by a titratable ketamine drip for the duration of surgery. Most received IV diazepam, 5-10 mg, immediately before induction.	Heart rate, RR, eye movements, the presence of laryngospasm, trismus, lacrimation, and excessive salivation were recorded prospectively. Psychiatric adverse event reporting is not presented, but the incidence of "hallucinations" was measured.	No cardiorespiratory adverse events occurred. Postoperative hallucinations were reported in all patients; the duration of postoperative h allucinations appeared to be shorter with premedicant diazepam.	Dysphoria and patient acceptance not distinguished from hallucinations.
12 [98]	Brewer CL, Davidson JR, Hereward S. Ketamine ("Ketalar"): a safer anaesthetic for ECT. Br J Psychiatry 120:559, 679-80(1972) eng.	28 psychiatric inpatients aged 18 to 67 undergoing a total of 86 electroconvulsive therapy sessions received IV ketamine, 2.2 mg/kg, (n = 38), IM ketamine, 4.4 mg/kg, (n = 24), or IV thiopentone, 4.5 mg/kg, (n = 24). All patients were taking their usual psychotropic medications.	No adverse event reporting methodology is presented.	No cardiorespiratory adverse events were reported. "In most cases, patients anesthetized with ketamine maintained an adequate airway in the supine position." No "hallucinatory or other emergence phenomena" occurred in this cohort.	Minimal methodology. Effect of patient's usual medications unknown. Emergency physicians unlikely to perform ECT.
13 [24]	Campbell G, Magee D, Kovacs J. Procedural sedation and analgesia in a Canadian Adult Tertiary Care Emergency Department: a case series. Can J Emerg Med 8:2, 85-93(2006) English.	A retrospectively generated (chart review) audit of procedural sedation practices in an adult tertiary-care center (n = 979) reported on 26 patients who received ketamine for a variety of ED procedures. Dosing information is not reported. Comedications included an unspecified benzodiazepine (n = 7), propofol (n = 3) and fentanyl (n = 2).	Cardiorespiratory status was monitored per local ED protocols. A prior definitions were used to define cardiorespiratory adverse events. No psychiatric adverse event reporting methodology is presented.	One ketamine patient comedicated with midazolam had an Sa_{O_2} <90%. No other cardiorespiratory adverse events are reported. One patient is reported to have had a postprocedure emergence reaction.	Chart review design. Dosing and route of administration not reported.

(continued on next page)

Table 1 (*continued*)

A	B	C	D	E	F
14 [68]	Caro DB. Trial of ketamine in an accident and ED. Anaesthesia 29:2, 227-9(1974) eng.	52 patients undergoing a variety of painful procedures in the ED received the minimum dose of IV ketamine that allowed for acceptable procedural conditions (45 patients received between 50 and 100 mg) as well as 10-20 mg IV diazepam, either before ketamine or before the conclusion of the procedure.	No adverse event reporting methodology is presented.	No cardiorespiratory adverse events occurred. No vomiting before recovery of consciousness occurred. Sixty-seven percent patients had no dreams, 25% had pleasant dreams, 6% had strange dreams, 2% had very unpleasant dreams. One additional patient had "considerable restlessness" while recovering, requiring the administration of additional diazepam followed by propanidid.	Loosely controlled noncomparative trial.
15 [74]	Cartwright PD, Pingel SM. Midazolam and diazepam in ketamine anaesthesia. Anaesthesia 39:5, 439-42(1984) eng.	60 patients undergoing short gynecologic procedures were randomized to receive either IV diazepam, 0.12 mg/kg, or midazolam, 0.07 mg/kg; all patients then received IV ketamine, 2 mg/kg.	Vital signs were measure every few minutes. Psychiatric adverse events were prospectively sought and recorded by MDs, RNs, and through a patient questionnaire given 12 hours postsurgery.	No cardiorespiratory adverse events occurred. No excitatory phenomena occurred during induction. Emergence delirium was present in 16.7% of midazolam patients vs 20% of diazepam patients; pleasant dreams, 20% vs 20%; unpleasant dreams, 6.7% vs 26.7%; nausea/vomiting, 20% vs 33.3%; patient acceptance, 100% vs 93.3%.	1 patient was withdrawn from the study because she was switched to halothane anesthesia the result of inadequate analgesia with ketamine.
16 [27]	Chudnofsky CR, Weber JE, Stoyanoff PJ, Colone PD, Wilkerson MD, Hallinen DL, Jaggi FM, Boczar ME, Perry MA. A combination of midazolam and ketamine for procedural sedation and analgesia in adult ED patients. Acad Emerg Med 7:3, 228-35(2000) eng.	70 patients undergoing painful procedures in the ED received IV midazolam, 0.07 mg/kg, followed 2 min later by IV ketamine, 2 mg/kg.	Cardiorespiratory status was continuously monitored by ED protocol and adverse events prospectively sought. Psychiatric adverse events prospectively sought according to criteria defined *a priori.*	No adverse cardiovascular events. Three apneic episodes, 2 of which required BVM ventilation. One episode of laryngospasm that required and responded to BVM ventilation. Five mild psychiatric adverse events requiring no treatment; no moderate or severe psychiatric adverse events. Patient acceptance 99%. Emesis occurred in 3% of patients.	No control group.

17	64	Coad NR, Mills PJ, Verma R, Ramasubramanian R. Evaluation of blood loss during suction termination of pregnancy: ketamine compared with methohexitone. Acta Anaesthesiol Scand 30:3, 253-5(1986) eng.	50 women undergoing elective termination of pregnancy were randomized to IV ketamine, 2 mg/kg, or methohexitone, 1 mg/kg. IV midazolam, 0.15 mg/kg, was administered 3 min before induction.	Adverse events, including cardiovascular and psychiatric adverse events, were specifically sought and recorded.	No cardiorespiratory or psychiatric adverse events in either group. The incidence of postoperative nausea was significantly higher in the ketamine group.	High premedicant midazolam dose.
18	81	Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg 45:1, 29-40(1966) eng.	130 patients aged 6 wk to 86 y undergoing a variety of procedures (including many intraoral procedures) were given IV or IM (small children) ketamine i n doses ranging from 1-2.2 mg/kg (IV) and 5.5-11 mg/kg (IM) for 15-60 s.	Cardiorespiratory parameters were prospectively measured and recorded. No psychiatric adverse event reporting methodology is presented.	Slight respiratory depression was noted in the first 30-60 s after IV administration, after that respiratory status returned to normal. No cardiorespiratory adverse events occurred. Psychiatric adverse events occurred are described but not quantified.	Uncontrolled study.
19	114	D'Angelo VF. Ketamine: a 5-year study. J Am Osteopath Assoc 77:3, 213-21(1977) eng.	Review of 851 cases where ketamine was given as the primary anesthetic to patients "chosen at random" for a wide variety of surgeries. Patients were premedicated with an assortment of agents, usually IV meperidine, 50 mg. Afterward, patients received IV ketamine 1. 65-2.2 mg/kg with smaller supplementary doses as needed.	Cardiorespiratory status was continuously monitored by sphygmomanometer, precordial stethoscope, and electrocardiogram by the anesthesiologist. No psychiatric adverse event reporting methodology is presented; detailed results appear to have been ascertained by chart review.	No cardiorespiratory adverse events are reported. Bad dreams or crying was documented in 6.2% of cases. Nausea or vomiting was documented in 1.3% of cases.	Review. Reactions to ketamine not documented in 14% of cases. Wide variety of premedicants.
20	116	Demling RH, Ellerbe S, Jarrett F. Ketamine anesthesia for tangenital excision of burn eschar: a burn unit procedure. J Trauma 18:4, 269-70(1978) eng.	45 burn patients undergoing 150 eschar excisions received IM ketamine, 4 mg/kg, with repeat dosing as necessary. "A type of music enjoyed by the patient" was played during the procedure.	No cardiorespiratory or psychiatric adverse event reporting methodology is presented.	No cardiorespiratory adverse events occurred. No severe psychiatric adverse events occurred. Approximately 10% of patients demonstrated "excitement and hallucinations" that resolved quickly with verbal support. Increasing doses were necessary in patients that required frequent procedures.	Semiquantitative, retrospective analysis.

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Table 1 (*continued*)

	A	B	C	D	E	F
21	71	Dundee JW, Lilburn JK. Ketamine-lorazepam. Attenuation of psychic sequelae of ketamine by lorazepam. Anaesthesia 33:4, 312-4(1978) eng.	185 patients undergoing short gynecologic procedures received either no premedication or lorazepam 4 mg by the oral, intramuscular, or intravenous route before administration of IV ketamine, 2 mg/kg or 1 mg/kg; 0.25 mg/kg ketamine boluses were given prn to maintain anesthesia.	Blood pressure was prospectively recorded; no other cardiorespiratory adverse event reporting methodology is presented. Postoperative vomiting, delirium, unpleasant dreams and patient acceptance were prospectively sought.	No cardiorespiratory adverse events are reported. Of the 50 patients who did not receive any premedication, postoperative nausea/vomiting occurred in 42, with a high prevalence of delirium and unpleasant dreams. Acceptance rate in this group was 24%. In all other groups, lorazepam by any route dramatically decreased all postoperative adverse events except nausea and vomiting, and patient acceptance was near 100%.	Unblinded study.
22	123	Ekele BA. Using ketamine for diagnostic laparoscopy. Nigeria Journal of Clinical Practice 3:5-7(2000) English.	Review of 134 consecutive gynecologic laparoscopies performed by the author in a Nigerian teaching hospital. Each patient received IV ketamine 1 mg/kg followed by half-dose supplements as needed.	No adverse event reporting methodology is presented, though the operations were carried out in "the main theater equipped with all resuscitative gadgets."	No cardiorespiratory adverse events were reported. One patient had tonic-clonic movements. Delirium, described as "incoherent verbal outbursts and restlessness" occurred in 10% of cases. Nausea or vomiting was reported in 5% of cases.	Limited methodology description in what appears to be a retrospective review.
23	62	Ellingson A, Haram K, Sagen N. Ketamine and diazepam as anaesthesia for forceps delivery. A comparative study. Acta Anaesthesiol Scand 21:1, 37-40(1977) eng.	26 patients undergoing forceps delivery were randomized to receive IV ketamine, 2 mg/kg, delivered for 30 s with additional smaller doses as needed postprocedure, or IV diazepam, 30 mg, in combination with nitrous oxide. In some cases the patient was premedicated with promethazine or meperidine during the first stage of labor.	No cardiorespiratory adverse event reporting methodology is presented, however the anesthesia was delivered by an anesthesiologist. The acceptability of the anesthesia to both patient and obstetrician was prospectively sought.	One patient from each group required a brief period of assisted ventilation because of apnea. Of 13 patients, 7 found recovery from ketamine to be unpleasant, whereas 0/13 patients found recovery from diazepam-N_20 to be unpleasant. There was no vomiting in either group.	No additional ketamine was given until the procedure was finished, therefore some patients were incompletely anesthetized at the end of the procedure.

24	84	Erbguth PH, Reiman B, Klein RL. The influence of chlorpromazine, diazepam, and droperidol on emergence from ketamine. Anesth Analg 51:5, 693-700(1972) eng.	300 patients undergoing therapeutic abortion were randomized to IV chlorpromazine, 10 mg, or placebo, followed 2 min later by IV ketamine, 1 mg/lb, given for 1 min. At the end of the procedure, patients were randomized to placebo, IV diazepam 5 mg, or IV droperidol, 5 mg. Smaller intraoperative ketamine doses were given as needed.	Cardiorespiratory status was continuously monitored. Adverse psychiatric events were prospectively sought in the operating room (OR), by trained ecovery room RNs, and by predischarge and 24 hour postoperative interviews.	One patient experienced laryngospasm; details were not provided. Postoperative vomiting occurred in no chlorpromazine-droperidol patients, up to 34% of placebo-placebo patients. Patient characterization of the anesthesia as good or excellent ranged from 58% in the placebo-placebo group to 78% in the placebo-diazepam group and the chlorpromazine-diazepam group.	Psychologically traumatic procedure.
25	124	Ersek RA. Dissociative anesthesia for safety's sake: ketamine and diazepam-a 35-year personal experience. Plast Reconstr Surg 113:7, 1955-9(2004) eng.	An account of one outpatient surgery center's experience with ketamine-diazepam anesthesia given to approximately 30 000 Patients for 35 y by a plastic surgeon without anesthesia MD or RN assistance. Each patient received PO diazepam, 20 mg, on arrival to the surgery center. Once in the operating suite, IM droperidol, 1.25 mg, IM was administered, followed by an IV diazepam infusion until the slurring of speech, followed by IV ketamine, 75 mg, slow infusion. Repeat doses of ketamine and diazepam were given according to need.	No adverse event reporting methodology is presented.	The author states that no untoward events occurred in his case series. He reports 2 hospital admissions (all other patients were discharged postoperatively). The first patient became excessively sedated after the second dose of ketamine, though Sa02 and BP remained normal throughout; she was admitted to the hospital for postoperative monitoring and discharged the following day. The second patient became excessively sedated with diazepam alone and was admitted postoperatively; she was also discharged without sequelae.	Descriptive review.

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Table 1 (*continued*)

	A	B	C	D	E	F
26	78	Ezri T, Szmuk P, Stein A, Konichezky S, Hagai T, Geva D. Peripartum general anasthesia without tracheal intubation: incidence of aspiration pneumonia. Anaesthesia 55:5, 421-6(2000) eng.	Historical review of 1870 patients undergoing peripartum operations, including 1496 patients who received IV diazepam, 0.05 mg/kg, and ketamine, 1 mg/kg, with additional bolus doses of ketamine, 0.2 mg/kg, as needed.	Aspiration, convulsions, apnea, postoperative dysphoria, postoperative vomiting, transient hypertension, and transient hypotension were specifically sought in this chart review.	No instances of aspiration, convulsions, or apnea during induction were found in the ketamine group. The incidence of postoperative dysphoria was 22.1%; 9.7% incidence of postoperative vomiting, 5.7% incidence of transient hypertension, and 2.1% incidence of transient hypotension.	Retrospective study with minimal chart review methodology described.
27	128	Feller, I. Anesthesia requirements for the severely burned patient, in status of ketamine in anesthesiology, 419-21. Ann Arbor, Michigan: NPP Books, 1990.	Brief historical account of more than 2000 procedures for more than 400 patients undergoing surgery related to burn injuries. These patients received an unspecified titrated dose of IV ketamine, which was often "less than the recommended dose" and repeated throughout the procedure as needed. IV diazepam was given in an unspecified dose before the procedure and before the last ketamine dose to avoid "psychologic aberrations after ketamine."	No adverse event reporting methodology is presented.	The author reports "excellent results" with "minimal complications." Supplemental oxygen is recommended in this report because "some patients have shallow respirations" during the procedures. An erythematous rash about the head, neck, and chest occurred in <5% of patients. The necessity of increasing the ketamine dose as tolerance develops in patients needing multiple procedures is noted.	Descriptive review.
28	80	Fine J, Finestone SC. Sensory disturbances following ketamine anesthesia: recurrent hallucinations. Anesth Analg 52:3, 428-30(1973) eng.	1400 patients received IV ketamine, 1-1.5 mg/kg, for unidentified surgical procedures. No standardized cotherapy methodology is presented.	No cardiorespiratory adverse event reporting methodology is presented. All patients were interviewed postoperatively and questioned with regard to the presence or absence of dreams, and, among patients who had dreams, if these dreams were pleasant or unpleasant.	No cardiorespiratory adverse events are reported. 20% of patients had no dreams. Of the 80% of patients who dreamed, 50% reported pleasant dreams and 30% reported unpleasant dreams. 3 patients reported occasional recurrent dreamlike hallucinations for 1 to 3 wk postoperatively.	Minimal methodology presented.

29 61	Freuchen I, Ostergaard J, Kühl JB, Mikkelsen BO. Reduction of psychotomimetic side effects of Ketalar (ketamine) by Rohypnol (flunitrazepam). A randomized, double-blind trial. Acta Anaesthesiol Scand 20:2, 97-103(1976) eng.	Randomized, double-blind trial (n = 136) where 69 patients undergoing therapeutic abortion received IV ketamine, 2 mg/kg, and flunitrazepam, 2 mg, mixed in the same syringe and injected for 60 s, and 67 patients received IV ketamine, 2 mg/kg, and placebo.	Cardiorespiratory parameters were continuously recorded. Psychiatric adverse events were prospectively assessed by observation and postoperative patient survey.	No cardiorespiratory adverse events occurred in either group; flunitrazepam attenuated the rise in blood pressure observed in the placebo group. Flunitrazepam greatly reduced the requirements for further intraoperative ketamine doses, as well as the incidence of postoperative confusion and motor restlessness. Of 66 patients in the placebo arm where data were available, 30 reported amnesia for dreams; 16 reported pleasant dreams and 20 reported unpleasant dreams, of which 12 were described as nightmares. Of 69 patients in the treatment arm, 68 reported amnesia for dreams and 1 reported pleasant dreams.	Flunitrazepam is no longer available in North America.
30 101	Galloon S. Ketamine for dilatation and curettage. Can Anaesth Soc J 18:6, 600-13(1971) eng.	272 women undergoing either diagnostic D and C or therapeutic abortion received IV ketamine, 2.2 mg/kg, and supplemental doses of 0.5 mg/kg as needed. Patients were divided into 5 roughly equal premedicant groups-all premedicants were given IM 90 min preprocedure. Groups included pantopon (an opioid), 0.286 mg/kg + scopolamine, 0.4 mg; pantopon + atropine, 0.6 mg; atropine only; scopolamine only; and diazepam, 0.143 mg/kg, + scopolamine. An additional 50 patients received supplemental nitrous oxide anesthesia.	No adverse event reporting methodology is presented though the study was carried out in an anesthesiologist-controlled OR setting. Furthermore, the results are presented to a degree of detail that suggests that both cardiorespiratory and psychiatric adverse events were prospectively sought.	No cardiovascular adverse events occurred. Systolic blood pressure and diastolic blood pressure increased in every patient within 2 minutes of ketamine injection, reaching maximum values in 10-15 min. HR increased in 95% of patients. Of 25 patients who received spirometry as part of the study, 11 became apneic for a period between 30 and 120 s. Four percent of patients required either jaw support for “obstructed breathing” or supplemental oxygen for “unsatisfactory color.” Unpleasant dreams occurred in 16.3% of patients, including 14.5% in the scopolamine-only group, 28% in the atropine-only group, and 5.8% in the diazepam-scopolamine group. The rate of unpleasant dreams did not vary between the abortion and diagnostic D	

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Table 1 (*continued*)

A	B	C	D	E	F
				and C group. Nausea or vomiting occurred in 41.5% of patients; this incidence was significantly reduced by scopolamine and scopolamine + diazepam, but not by atropine. A rash appeared in 17% of patients, this disappeared within 15-20 min and did not recur with repeat ketamine administrations.	
31 92	Garfield JM, Garfield FB, Stone JG, Hopkins D, Johns LA. A comparison of psychologic responses to ketamine and thiopental-nitrous oxide-halothane anesthesia. Anesthesiology 36:4, 329-38(1972) eng.	48 servicemen undergoing skin grafting or minor orthopedic procedures were randomized to receive IV ketamine (mean dose 1.6 mg/kg for 90 s) with additional doses as necessary or thiopental-nitrous oxide-halothane anesthesia. In addition, each group was divided into a "minimal briefing" or "detailed briefing" subset, where either a few details or a complete account of the expected anesthetic side effects were discussed with the patient preoperatively.	No cardiorespiratory adverse event reporting methodology is presented. Preoperative "baseline anxiety" levels were assessed by a standardized scale. Psychiatric adverse events were prospectively sought and recorded in a detailed, standardized patient survey.	No cardiorespiratory adverse event data are presented. The incidence of postoperative anxiety was 9/24 ketamine patients, who showed no correlation to preoperative anxiety levels. Of 24 ketamine patients, 4 expressed dissatisfaction with the anesthetic technique. In the thiopental group, postoperative anxiety occurred in 3/24 patients and dissatisfaction occurred in 1/24 patients.	
32 126	Ginsberg H, Gerber JA. CI-581: a clinical report on 100 patients. S Afr Med J 42:43, 1177-9(1968) eng.	100 patients undergoing minor surgical procedures received IV ketamine, most often at a dose of 1.5 mg/kg with smaller supplemental doses as needed. In 11 cases, supplemental anesthesia (usually with nitrous oxide) was given.	Cardiorespiratory and psychiatric adverse events were prospectively recorded, including a formal acceptance evaluation on the day after the anesthetic in 55 patients.	No cardiorespiratory adverse events occurred. Mean SBP elevation was 31 mm Hg, DBP elevation 26.6 mm Hg. Mean heart rate elevation was 22 beats per minute. Tachynpnea "often occurred," and 30 s of apnea was noted in one patient. Mild hallucinations were noted in 3 patients, and patient acceptance was 96%. Postoperative nausea occurred in 2% of patients.	Incompletely controlled prospective series.

33	60	Gjessing J. Ketamine (Cl-581) in clinical anaesthesia. Acta Anaesthesiol Scand 12:1,15-21(1968) eng.	40 elderly patients undergoing a variety of surgeries (including abdominal operations, hip fractures, and amputations) received ketamine, 1 mg/kg, with additional half-doses given as needed. An unspecified proportion of patients received placebo, and some were premedicated with promethazine. Eleven patients received supplementary anesthesia.	Detailed cardiorespiratory and metabolic measurements were taken prospectively. A structured cognitive evaluation was undertaken preanesthesia and postanesthesia, but no psychiatric adverse event reporting methodology is presented.	67% of patients were age >75. No cardiorespiratory or psychiatric adverse events were reported in this cohort. Authors conclude that anesthetic results improve with increasing age.	Methodology is detailed but confusing and incomplete.
34	4	Green SM, Clem KJ, Rothrock SG. Ketamine safety profile in the developing world: survey of practitioners. Acad Emerg Med 3:6, 598-604(1996) English.	Survey of 175 missionary physicians addressing clinical experience with ketamine in the developing world.	Survey specifically assessed monitoring and adverse events.	19 serious complications reported by 55 respondents in an estimated 12 844 cases, most that did not result in adverse sequelae. Basic mechanical monitoring was used in a minority of cases, and often the person administering ketamine was also performing the procedure.	Survey design. Exact clinical circumstances, including the use of cotherapies, not necessarily recalled by respondent.
35	26	Green SM, Rothrock SG, Hestdalen R, Ho M, Lynch EL. Ketamine sedation in mentally disabled adults. Acad Emerg Med 6:1, 86-7(1999) eng.	As part of a much larger pediatric study, 17 mentally disabled adults (median age 28) received IM ketamine, 2.9-4.7 mg/kg (n = 15), or IV ketamine, 1 mg/kg (n = 2), for a variety of ED procedures. Five of these patients received concurrent midazolam.	Cardiorespiratory function and the occurrence of psychiatric adverse events were continuously monitored per ED ketamine protocol.	No cardiovascular adverse events occurred. “Soft stridor” and oxygen desaturation to 88% occurred in 1 patient, which resolved with airway repositioning. Brief “possible seizures” occurred in 3 patients, all known for seizures, 2 of whom were known for daily seizures; these episodes resolved without treatment. Postemergence emesis occurred in 3 patients. No recovery hallucinations or agitation occurred in this cohort.	

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	A	B	C	D	E	F
36	65	Green SM, Sherwin TS. Incidence and severity of recovery agitation after ketamine sedation in young adults. Am J Emerg Med 23:2, 142-4(2005) English.	Prospective case series of 26 patients aged 16-21 undergoing painful procedures in the ED. Patients received opioid analgesia as needed before the painful procedure. IV ketamine was administered as determined by the treating physician in doses ranging between 1.0 and 1.9 mg/kg with a mean of 1.3 mg/kg. No benzodiazepines were administered at any time.	Airway complications, hypersalivation, emesis, and the adequacy of sedation were prospectively assessed. Agitation, crying, and npleasant hallucinations or nightmares during recovery were each prospectively recorded on a visual analog scale by the provider.	No airway complications or hypersalivation occurred. Emesis was reported in 2 patients and an urticarial rash occurred in one patient. One patient had recovery agitation and one patient had recovery crying; in both cases symptoms resolved without treatment and patients were calm at the time of discharge. No unpleasant hallucinations or nightmares occurred.	Small series.
37	103	Hejja P, Galloon S. A consideration of ketamine dreams. Can Anaesth Soc J 22:1, 100-5(1975) English	150 patients undergoing dilation and curettage received pantopon (an opioid), 0.28 mg/kg, 90 min before induction with IV ketamine, 2.2 mg/kg. Anesthesia was maintained with repeat ketamine doses, 0.5 mg/kg. Patients were divided into 3 groups: controls, patients blindfolded during the procedure, and patients blindfolded during the procedure and until return of consciousness.	Vital signs were continuously monitored. Psychiatric adverse events were prospectively sought by a study investigator during the procedure, during recovery by a nurse observation protocol, as well as a formal assessment by one of the study investigators postrecovery.	No adverse cardiorespiratory adverse events are reported. 11% of patients had unpleasant dreams; this did not vary significantly among the 3 groups. 75% of patients who identified themselves as home-dreamers dreamed under ketamine; 2% of patients who identified themselves as non–home-dreamers dreamed under ketamine. 98% of patients reported that they would have the same anesthetic again or did not care; 2% of patients reported that they would not like to have the same anesthetic again.	Pantopon is not commonly used in modern EM practice.
38	83	Hervey WH, Hustead RF. Ketamine for dilatation and currettage procedures: patient acceptance. Anesth Analg 51:4, 647-55(1972) eng.	151 patients undergoing therapeutic abortion were randomized to IV ketamine, 100 mg, with subsequent 50 mg doses as needed (n = 53); IV thiopental, 150 mg, followed by IV ketamine, 100 mg, and nitrous oxide with subsequent thiopental as needed (n = 37); or IV	No cardiorespiratory adverse event reporting methodology is presented. Adverse psychiatric events were prospectively sought in the OR, by trained recovery room RNs, and by predischarge postoperative interviews.	No cardiorespiratory adverse events are reported. Postoperative nausea or vomiting was present in 57% of group I (ketamine only), 35% of group II (ketamine-thiopental-NO_2), and 23% of group III (thiopental-NO_2). Unpleasant dreams were reported in 32% of group I,	Psychologically traumatic procedure.

			thiopental, 150 mg, followed by nitrous oxide with subsequent thiopental as needed (n = 61). Patients in the last group were paralyzed and intubated.		8% of group II, and no patients in group III. Patients rejected the anesthetic technique in 42% of group I, 32% of group II, and 5% of group III.	
39	115	Ikechebelu JI, Udigwe GO, Obi RA, Joe-Ikechebelu NN, Okoye IC. The use of simple ketamine anaesthesia for days—case diagnostic laparoscopy. J Obstet Gynaecol 23:6, 650-2(2003) English.	295 women undergoing diagnostic laparoscopy were randomized to receive IV ketamine, 1 mg/kg (n = 117); IV ketamine, 1 mg/kg + diazepam, 10 mg (n = 76); or IV ketamine + promethazine, 50 mg (n = 102).	Vital signs were continuously monitored. Postoperative adverse events such as vomiting, talkativeness, restlessness, dizziness, and idiosyncratic reactions were prospectively assessed.	There were no reported cardiorespiratory adverse events in any group. In the ketamine only group, 15% of patients had emergence delirium, 6% nausea/vomiting. 1 patient had breathlessness and air hunger and one had tonic-clonic movements; both responded to diazepam. In the ketamine-diazepam group, 1% of patients had emergence delirium, 7% had nausea/vomiting, and the mean recovery time was prolonged from 45-200 min. In the ketamine-promethazine group, 3% had emergence delirium and 1% had nausea/vomiting, with a mean recovery of 70 min.	Dysphoria and patient acceptance not distinguished from emergency delirium.
40	105	Joly LM, Benhamou D. Ventilation during total intravenous anaesthesia with ketamine. Can J Anaesth 41:3, 227-31(1994) English.	76 patients undergoing a variety of surgeries were given IV diazepam, 0.1 mg/kg, and ketamine, 2.5 mg/kg, and randomized to supplemental oxygen and room air.	Study specifically assessed pulse oximetry readings over the course of the surgery and recovery. Psychiatric adverse event reporting is not presented.	Desaturation was more common in the room air group than the supplemental oxygen group. Two patients required endotracheal intubation for apnea associated with generalized rigidity.	Both adverse events were in obese patients, note medications dosed per kilogram.
41	136	Kamm GD. Ketamine anaesthesia by continuous intravenous drip. Trop Doct 8:2,68-72(1978) eng.	50 patients undergoing a variety of surgical procedures received PO haloperidol, 0.1 mg/kg, maximum 5 mg 1 h before induction of anesthesia with an IV ketamine drip (rate not quantified) that was maintained until several minutes before the completion of the procedure. Average ketamine dose was 4-6 mg/kg per hour.	Cardiorespiratory status was continuously monitored. No psychiatric adverse event reporting methodology is presented.	No cardiorespiratory adverse events occurred. Psychiatric adverse events are not commented upon.	Minimal methodology presented in this brief report.

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Table 1 (*continued*)

	A	B	C	D	E	F
42	134	Ketcham DW. Where there is no anaesthesiologist: the many uses of ketamine. Trop Doct 20:4, 163-6(1990) English.	Historical account of approximately 8000 patients who received ketamine for various surgical and nonsurgical procedures for a 15-y period in a rural mission hospital in southern Bangladesh. Diazepam premedication was given 2.2 mg/kg PO 1 h preprocedure or IV near the time of induction. Patients received IV ketamine, 2.2 mg/kg, or IM 4.4 mg/kg. The same provider typically administered the anesthesia and performed the surgical procedure.	No adverse event reporting methodology is presented.	A single anesthetic death was reported, when a mother was allowed to hold her child before recovery from anesthesia, and the child was held in a neck-flexed position. No other adverse events were reported. Specifically no laryngospasm occurred, despite ketamine technique being used many times for esophagoscopy and bronchoscopy.	Descriptive review.
43	90	King, Steven. A new intravenous or intramuscular anesthetic. Anesthesiology 28:258(1967) English.	Brief historical account of 106 patients undergoing unspecified operations who received ketamine either IV (n = 56) or IM (n = 38) or IM followed by IV (n=12), at a dose of 2.2 mg/kg. Further half-doses were given as needed.	No adverse event reporting methodology is presented though the study was carried out in an anesthesiologist-controlled OR setting.	No cardiorespiratory adverse events occurred. "There was a noticeable but not disturbing depression of the respiration for 2 to 3 min." Psychiatric adverse events were not quantified, but "About 50% of the adults had definite hallucinations, often of a terrifying nature." No postoperative vomiting occurred.	Brief review, minimal methodology. Dysphoria and patient acceptance not distinguished from postoperative hallucinations.
44	102	Krestow M. The effect of postanaesthetic dreaming on patient acceptance of ketamine anaesthesia: a comparison with thiopentone-nitrous oxide anaesthesia. Can Anaesth Soc J 21:4, 385-9(1974) English.	100 patients undergoing therapeutic abortion alternated between 2 groups: One group received IV ketamine, 2 mg/kg, at induction and 1 mg/kg at the time of cervical dilation; the other group received thiopentone, 5 mg/kg, and a nitrous oxide/oxygen mixture at induction with additional thiopentone, 1.7 mg/kg, at cervical dilation. All patients received 10 mg droperidol 60 min before surgery.	Cardiorespiratory adverse event reporting methodology is not presented though the study was carried out in an anesthesiologist-controlled OR setting. 12 to 24 hours postprocedure, patients were specifically questioned by an anesthesiologist about their dreams and acceptance of the anesthetic technique.	No cardiorespiratory adverse events are reported in either group. The incidence of unpleasant dreams after ketamine was 36%. No patient in the thiopentone group had an unpleasant dream. 34% of patients in the ketamine group rejected ketamine as an agent for future surgery; all patients in the thiopentone group accepted their anesthetic for future surgery.	Psychologically traumatic procedure.

45	75	Kumar A, Bajaj A, Sarkar P, Grover VK. The effect of music on ketamine induced emergence phenomena. Anaesthesia 47:5, 438-9(1992) English.	50 women undergoing short gynecological procedures were given IM morphine .15 mg/kg and promethazine, 0.4 mg/kg, 1 h before induction with IV ketamine, 2 mg/kg. Patients were then randomized to listen to silent headphones or music of their choice for 5 min before induction and 15 min after the completion of the procedure.	Cardiorespiratory adverse event reporting is not presented. Adverse psychiatric events were specifically sought by survey on postoperative day 2.	Of controls, 13 found ketamine anesthesia acceptable and 8 not acceptable. 20 patients in the music group found ketamine anesthesia acceptable and 1 unacceptable.	Presence of silent headphones on emergence might be disconcerting to some patients.
46	77	Lederer W. Peripartum general anaesthesia without tracheal intubation. Anaesthesia 55:11, 1140(2000) English.	Historical account of patients undergoing 65 operations and 347 minor surgical interventions in a Ugandan hospital. Patients received IV ketamine, 0.5 mg/kg, followed by 0.25 mg/kg doses every 10-15 min prn.	Monitoring was "restricted to intermittent measurement of blood pressure, pulse rate, and respiratory rate."	No cardiorespiratory adverse events occurred. "Frightening hallucinations were infrequent, and, when present, not completely controlled by benzodiazepines."	Descriptive review.
47	70	Lilburn JK, Dundee JW, Nair SG, Fee JP, Johnston HM. Ketamine sequelae. Evaluation of the ability of various premedicants to attenuate its psychic actions. Anaesthesia 33:4, 307-11(1978) eng.	315 patients undergoing minor gynecologic procedures were randomized to receive one of 14 premedicant regimens, including saline placebo, 10-40 min before induction. The treating anesthesiologist was blinded to the group allocation. All patients then received IV ketamine, 2 mg/kg, for induction, with additional 0.25 mg/kg boluses as needed. Premedicant regimens included varying combinations of diazepam, flunitrazepam, lorazepam, fentanyl, trifluoperazine, pentobarbital, hydroxyzine, meperidine and promethazine.	Cardiorespiratory monitoring was in place per operating room protocols. Psychiatric adverse events and patient acceptability were prospectively sought by standardized methodology.	No cardiorespiratory adverse events were reported. The incidence of unpleasant dreams and degree of patient acceptability varied widely across the premedicant regimens. Of 5 patients who received placebo, 2 reported unpleasant dreams and 1 patient accepted the anesthetic technique. Of the treatment groups, IV lorazepam 4 mg provided the most consistent improvement in patient acceptance, with a complete abolition of unpleasant dreams and 100% patient acceptance if given 30-40 min before induction. A significant prolongation of recovery time was associated with lorazepam premedication.	Large number of treatment groups.

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A	B	C	D	E	F
48 97	Lilburn JK, Dundee JW, Nair SG. Attenuation of psychic sequelae from ketamine [proceedings]. Br J Clin Pharmacol 4:5, 641P-2P(1977) eng.	255 patients undergoing minor gynecological procedures received an intravenous premedicant 10 min before receiving IV ketamine, 2 mg/kg, for induction with smaller repeat doses as necessary. Premedicants included saline placebo; diazepam, 15 mg and 0.2 mg/kg; flunitrazepam, 1.5 mg and 0.02 mg/kg; lorazepam, 4 mg; droperidol, 5 mg; droperidol, 5 mg with fentanyl, 0.1 mg; pentobarbital, 100 mg; hydroxyzine, 100 mg; meperidine, 100 mg; and promethazine, 25 mg.	No cardiorespiratory adverse event reporting methodology is presented. Psychiatric adverse events were prospectively assessed and evaluated in a postoperative survey.	No cardiorespiratory adverse event data are presented. 35% of patients who received placebo had unpleasant dreams, and 64% found the anesthetic unacceptable. All premedicants reduced psychiatric adverse events and increased patient acceptability. The lorazepam and flunitrazepam premedicants offered the greatest reduction in unpleasant dreams and improvement in anesthesia acceptability. Based on these results, the authors administered IV lorazepam 4 mg to 155 additional patients 30 min preinduction and report 100% anesthetic acceptability in this cohort.	Minimal methodology presented in this brief report.
49 89	Lorhan PH, Lippman M. Clinical appraisal of the use of ketamine hydrochloride in the aged. Anesth. Analg. (Cleveland) 50: May-Jun, 448-51(1971)	87 patients of average age 84 (including 3 patients aged more than 100) undergoing 91 surgical procedures received a variable dose of droperidol before IV ketamine, 2.2 mg/kg, supplemented with smaller doses as needed intraoperatively.	No adverse event reporting methodology is presented though the study was carried out in an anesthesiologist-controlled OR setting.	There were no ASA class I or II operations; 22 operations were ASA class III, 55 class IV, and 14 class V. Anesthesia was supplemented with other agents intraoperatively in 4 cases. Five perioperative deaths occurred, none attributed to the anesthetic. 9 cases of severe hypertension occurred,	Minimal methodology presented. Extraordinarily high-risk patients in this series.

				treated successfully with reserpine. No other actionable or clinically significant adverse event is reported.	
50 88	Maduska AL, Hajghassemali M. Arterial blood gases in mothers and infants during ketamine anesthesia for vaginal delivery. Anesth Analg 57:1, 121-3(1978) eng.	10 patients presenting with active labor received ketamine, 1 mg/kg, by slow intravenous injection. An arterial blood gas sample was obtained at the time of delivery or 3 min postinjection, whichever came first. This experimental group was compared against 10 control patients who received 50 mg meperidine and spinal anesthesia for labor. Arterial blood gas samples were sent from this group at the time of delivery.	No adverse event reporting methodology is presented, though all patients received routine perinatal hemodynamic monitoring.	There were no cardiorespiratory adverse events. There was no difference between controls and the ketamine group in either mothers or infants with regard to pH, Pco_2, Po_2, and Apgar scores. Two patients in the ketamine group "seemed restless" after delivery and were successfully managed with 10 mg IV diazepam.	
51 79	Mattila MA, Larni HM, Nummi SE, Pekkola PO. Effect of diazepam on emergence from ketamine anaesthesia. A double-blind study. Anaesthesist 28:1, 20-3(1979) eng.	109 patients undergoing dilation and curettage received morphine 8-14 mg 1 h before receiving IV ketamine 1.5 mg/kg at induction. With the ketamine bolus, 55 patients were randomized to receive IV diazepam 10 mg and 54 patients were randomized to placebo. Supplemental ketamine was given 0.2-0.4 mg/kg prn. Most patients received methylergotamine 0.2 mg IV at the end of the procedure.	Cardiorespiratory adverse event reporting methodology is not presented though the study was carried out in an anesthesiologist-controlled OR setting. Psychiatric adverse events were prospectively sought by both physician and nurse in postoperative assessment.	No cardiorespiratory adverse events are reported. 20% of patients in the placebo group had unpleasant dreams/experiences, compared to 6% of patients in the diazepam group. Nausea or vomiting was present 2% of diazepam-treated patients compared to 24% of controls.	The postprocedure use of methylergotamine is unlikely in EM practice. Patient's subjective acceptance of ketamine not reported.

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Table 1 (*continued*)

	A	B	C	D	E	F
52	96	Moore J, McNabb TG, Dundee JW. Preliminary report on ketamine in obstetrics. Br J Anaesth 43:8, 779-82(1971) eng.	75 patients undergoing minor obstetric operations received IV ketamine, 2 mg/kg, followed by smaller doses as needed. Premedicants varied and included diazepam, meperidine pentazocine, papaveratum, and pentobarbital.	Cardiorespiratory status was continuously monitored. Psychiatric adverse events were prospectively sought.	No cardiorespiratory adverse events occurred. Unpleasant dreams occurred in 8% of patients; 3/75 patients reported the anesthetic unacceptable.	Varying, uncontrolled premedicants.
53	67	Morgan M, Loh L, Singer L, Moore PH. Ketamine as the sole anaesthetic agent for minor surgical procedures. Anaesthesia 26:2, 158-9(1971) eng.	138 patients aged 2 mo to 89 y undergoing minor surgical procedures received IV ketamine, 2.2 mg/kg, for 45-60 s or IM ketamine, 10-12 mg/kg, with incremental IV doses given as needed. Premedicants were not controlled and variously included papaveratum, droperidol, diazepam, and "miscellaneous" agents.	Cardiorespiratory and psychiatric adverse events were prospectively sought in the OR and recovery room.	There were no cardiovascular adverse events. Airway obstruction occurred in 11.5% of patients, all of which responded to airway repositioning maneuvers or the insertion of an oropharyngeal airway. 10% of patients reported frightening dreams; 2 patients required diazepam sedation postoperatively. Postoperative vomiting occurred in 4.2%.	Uncontrolled study with widely varying premedicant regimens.
54	106	Nanayakkara B. Maintenance of oxygenation during total intravenous anaesthesia with ketamine while breathing air. Ceylon Med J 39:4, 160-2(1994) English.	65 patients undergoing minor surgical procedures in Sri Lankan hospital received IV diazepam, 0.1 mg/kg, followed by IV ketamine, 2 mg/kg, given for 1 min. Half-dose ketamine supplements were given as needed.	Cardiorespiratory status was continuously monitored. Patients were prospectively assessed for "hallucinations."	No cardiovascular adverse events occurred. 7.6% of patients showed a fall in Sao_2 to <90% after ketamine administration; of these 3/5 required a jaw-thrust maneuver to maintain a patent airway. Upper airway obstruction appears to have been diagnosed based on snoring. Postoperative	Dysphoria and patient acceptance not distinguished from postoperative hallucinations.

					hallucinations occurred in 7.6%, and vomiting occurred in 12%.	
55	131	Odetoyinbo O. Ketamine: Parenteral anaesthesia for tonsillectomy. Trop Doct 17:1, 21-2(1987) eng.	67 patients aged 6-43 y undergoing tonsillectomy at a Nigerian hospital received IV diazepam, 0.2 mg/kg (max 10 mg) 5-10 min preinduction. The pharynx was then anesthetized with 3-4 doses of 10% lidocaine spray (10 mg/dose). Patients then received IM ketamine 5 mg/kg and were positioned in neck hyperextension with sandbags under the shoulders so that blood would flow anteriorly rather than posteriorly. An additional dose of IV ketamine, 1 mg/kg, was given just before the commencement of the operation.	Cardiorespiratory status was continuously monitored by a nurse anesthetist. No psychiatric adverse event reporting methodology is presented.	No cardiorespiratory adverse events occurred; specifically there were no cases of laryngospasm. No "emergency delirium" occurred, but "patients were rather more restless than usual." The authors note a prolonged recovery time ranging from 40 min to 2 h. Postoperative vomiting occurred in 31% of patients.	Protective effect of lidocaine is unknown, as there was no control group who did not receive lidocaine spray. Dysphoria and patient acceptance not distinguished from emergence reactions.
56	118	O'Dowd MJ, Sil B. Ketalar its use by a single operator. Med J Zambia 11:5, 151-3(1977) English.	50 patients with retained products of conception undergoing uterine evacuation in a Zambian hospital received IV ketamine, 2 mg/kg. Anesthesia and operative procedure was performed by the same provider.	Cardiorespiratory status was continuously monitored. No psychiatric adverse event reporting methodology is presented.	No cardiorespiratory adverse events occurred. 20% of patients had unpleasant dreams. Postoperative emesis occurred in one patient.	
57	100	Oduntan SA, Gool RY. Clinical trial of ketamine (CI-581): a preliminary report. Can Anaesth Soc J 17:4, 411-6(1970) eng.	100 patients undergoing various surgical procedures received 1-1.25 mg/kg IV ketamine followed by a ketamine infusion or smaller boluses as needed.	Cardiorespiratory status was continuously monitored. No psychiatric adverse event reporting methodology is presented.	No cardiorespiratory adverse events are reported. Limb movements occurred in 12% of patients; limb	Limited methodology description.

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Table 1 (*continued*)

A	B	C	D	E	F
				rigidity 15%, nausea/ vomiting in 4%. Restlessness was observed postoperatively in 5% of patients with hallucinations in 2%. Of hallucinations in 2 patients, in one patient were they described as frightening.	
58 66	Paix BR, Capps R, Neumeister G, Semple T. Anaesthesia in a disaster zone: a report on the experience of an Australian medical team in Banda Aceh following the "Boxing Day Tsunami." Anaesth Intensive Care 33:5, 629-34(2005) English.	117 patients undergoing mostly lower extremity wound-related surgeries after a natural disaster in Indonesia received either IV midazolam, 5 mg, or diazepam, 2 to 5 mg,a "small intravenous morphine dose at the anesthetist's discretion," and ketamine, 80-100 mg, with quarter-dose boluses of ketamine as well as "further benzodiazepines and opioids as necessary" to maintain adequate surgical conditions.	No adverse event reporting methodology is presented.	"Oximeter readings generally dipped to around 90% after induction, then rapidly rose to exceed 95%." "Only 4 of 117 spontaneously ventilating patients required temporary jaw support and a further 2 required oral airways." "Approximately one patient in 10 appeared to have unpleasant psychic phenomena."	Descriptive review.
59 76	Pederson L, Benumof J. Incidence and magnitude of hypoxaemia with ketamine in a rural African hospital. Anaesthesia 48:1, 67-9(1993) English.	23 Kenyan patients undergoing a variety of minor surgical procedures received ketamine either IV 2 mg/kg or IM 8 mg/kg with additional IV boluses 0.5 mg/kg as needed. Sao_2 was continuously monitored. Age range was 4 mo to 60 y; 12 patients were younger than 10 y of age.	Study specifically assessed pulse oximetry readings over the course of the surgery and recovery. Psychiatric adverse event reporting methodology is not presented.	Mean Sao_2 values reached their nadir (90.8%) in the first minute after induction. In 4 patients, Sao_2 dropped <90%; 2 patients <85%; 2 patients <75%. In all cases, saturations returned to normal spontaneously with supplemental oxygen.	Elevation 6000 feet, Pio_2 127 mm Hg.

60	104	Pesonen P. Pulse oximetry during ketamine anaesthesia in war conditions. Can J Anaesth 38:5, 592-4(1991) English.	65 war-wounded patients were given IV diazepam, 0.1 mg/kg, and ketamine, 2 mg/kg, followed by a titratable ketamine drip for the duration of surgery. Pulse oximetry measurements were recorded throughout.	Study specifically assessed pulse oximetry readings over the course of the surgery and recovery. Psychiatric adverse event reporting methodology is not presented.	Of 57 analyzable results, 6 patients had brief periods of saturation <90%, including 2 patients who had periods of saturation <80% associated with snoring. All 6 patients responded to airway repositioning measures.	No control group.
61	109	Porter K. Ketamine in prehospital care. Emerg Med J 21:3, 351-4(2004) eng.	Historical account of 32 patients aged 9-87 undergoing various prehospital management procedures including extrication, limb reduction/ splintage, and in one case an above-knee amputation. Patients received IV ketamine, 20, 25, 50 or 100 mg, initially, with additional 20, 25, or 50 mg doses given as needed. Patients received IV midazolam, 0.5-2 mg, as needed for psychiatric distress on emergence.	Cardiorespiratory status was continuously monitored. No psychiatric adverse event reporting methodology is presented.	There were no cardiovascular adverse events, including in 2 patients who were hypotensive on EMS arrival. In these 2 patients SBP was maintained and not increased. Hypersalivation occurred in one instance, the 9-y-old child, but was "not a clinical problem." No other respiratory adverse events occurred. Midazolam was given in 12/32 patients who were recovering from ketamine administration and exhibited "aggression or agitation."	
62	117	Roberts JR, Geeting GK. Intramuscular ketamine for the rapid tranquilization of the uncontrollable, violent, and dangerous adult patient. J Trauma 51:5, 1008-10(2001) eng.	Case report describing an uncontrollably violent cocaine-intoxicated HIV-positive 28-y-old man who used a spurting ulnar artery laceration as a weapon. The patient was temporarily restrained and received	Continuous cardiorespiratory monitoring was instituted as soon as feasible postinjection. No psychiatric adverse event methodology is presented.	The patient entered a tranquil/dissociative state within 2-3 min postinjection and was then able to be managed conventionally. Transient hypertension and tachycardia occurred without sequelae.	Case report design.

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Table 1 (*continued*)

A	B	C	D	E	F
		IM ketamine, 5 mg/kg; several minutes later the patient received IM lorazepam, 4 mg.		No cardiorespiratory or psychiatric adverse events occurred in this case. Follow-up psychiatric and laboratory assessment was unremarkable.	
63 69	Roopnarinesingh S, Kalipersadsingh S. Manual removal of the placenta under ketamine. Anaesthesia 29:4, 486-8(1974) eng.	Apparently prospective evaluation of 30 patients undergoing surgery for retained placenta in Trinidad. Each patient received IV diazepam 10 mg or IV chlorpromazine, 25 mg, 3-5 min before induction with IV ketamine, 100 mg. No anesthesiologist was present, but the surgeon had a junior physician assistant.	"Each patient's airway and vital signs were supervised by the house-officer." No psychiatric adverse event reporting methodology is presented, but "any adverse reactions" were prospectively recorded.	No adverse cardiorespiratory events occurred. "Hallucinations in the form of pleasant dreams" were present in 2 patients, and one patient became "arrogant" on emergence.	Dysphoria and patient acceptance not distinguished from postoperative hallucinations.
64 23	Sacchetti A, Senula G, Strickland J, Dubin R. Procedural Sedation in the Community Emergency Department: Initial Results of the ProSCED Registry. Acad Emerg Med (2007) ENG.	A prospectively generated procedural sedation registry (n = 1028) reported on 145 patients who received ketamine for a variety of ED procedures. Dosing and comedication information is not reported.	Cardiorespiratory status was monitored per local ED protocols; cardiorespiratory adverse events and the presence of "agitation" were prospectively recorded on structured forms.	Ketamine use was associated with a single undefined adverse event (0.7%), which was the lowest adverse event rate of all agents included in the study that are typically used for procedural sedation. 83% of procedural sedations in this series were carried out by a single operator.	Uncontrolled use study. Dosing, route, and nature of adverse event not reported.
66 91	Sears BE. Complications of ketamine. Anesthesiology 35:2, 231(1971) English.	Case report in the form of letter to editor.	None.	"Hypoxic cardiac arrest secondary to respiratory depression has been observed in a debilitated adult."	No further information is provided.
67 73	Sklar GS, Zukin SR, Reilly TA. Adverse reactions to ketamine	90 patients undergoing a variety of minor surgical procedures received a	Cardiorespiratory parameters were monitored as per	No cardiorespiratory adverse events were reported. The rate of	Uncontrolled study with widely varying premedicant regimens.

		anaesthesia. Abolition by a psychological technique. Anaesthesia 36:2, 183-7(1981) eng.	focused interview by a trained provider where anesthetic expectations were discussed and patients advised that they may experience vivid hallucinations, the content of which they could determine. Approximately half the patients then received "a wide variety" of premedications as determined by the anesthesiologist; all patients received IV ketamine, 1-2 mg/kg, with supplemental doses as needed.	operating room protocol. Psychiatric adverse events were prospectively sought and formally assessed by the treating anesthesiologist based on a predetermined instrument.	dreaming was between 30% and 45%. No patients had unsatisfactory dreams and no patients were unwilling to have ketamine anesthesia again.	
68	72	Spreadbury TH. Anaesthetic techniques for surgical correction of fractured neck of femur. A comparative study of ketamine and relaxant anaesthesia in elderly women. Anaesthesia 35:2, 208-14(1980) eng.	30 elderly women (10 younger than 80 y and 20 women older than 80 y) undergoing femoral neck fracture repair received ketamine IV, 2 mg/kg, with supplemental half doses as needed. Patients in pain preoperatively were given "an analgesic" and oral diazepam, 5-10 mg, was given if received "relaxant" anesthesia, usually consisting of thiopentone with a paralytic and volatile anesthetic.	This study was primarily designed to assess short-term outcomes, but cardiorespiratory and psychiatric adverse events were prospectively sought and recorded, including a battery of sophisticated postoperative mental and physical functioning tests.	No adverse cardiorespiratory events occurred intraoperatively or in the immediate postoperative period. One patient in the ketamine group died in the first 15 d (attributed to wound abscess and septicemia), compared to 7 in the relaxant group. More late deaths occurred in the ketamine group, however, so that the final survival rate was equal. Of the 30 ketamine patients, 5 had hallucinations or dreams, but no unpleasant dreams. Of 30 relaxant patients,	Dysphoria and patient acceptance not distinguished from postoperative hallucinations.

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Table 1 (*continued*)

A	B	C	D	E	F
				4 had hallucinations or dreams, with one patient having a terrifying dream. The operating conditions were noted to be superior with relaxant anesthesia.	
69 63	Stefánsson T, Wickström I, Haljamäe H. Hemodynamic and metabolic effects of ketamine anesthesia in the geriatric patient. Acta Anaesthesiol Scand 26:4, 371-7(1982) eng.	8 patients of average age 83 undergoing surgical correction of a hip fracture received IV droperidol, 2.5 mg, followed 30 min later by slow IV injection of ketamine until the patient was unable to react to verbal command (mean dose 1.75 mg/kg, delivered for 2 min). Anesthesia was supplemented by a continuous infusion of ketamine, titrated to effect.	Numerous cardiorespiratory and metabolic parameters were prospectively examined. No psychiatric adverse event reporting methodology is presented.	No cardiorespiratory or psychiatric adverse events occurred.	Small, uncontrolled study.
70 110	Streatfeild KA, Gebremeskel A. Arterial oxygen saturation in Addis Ababa during diazepam-ketamine anaesthesia. Ethiop Med J 37:4, 255-61(1999) English.	46 patients undergoing minor surgical procedures received IV diazepam, 0.1-0.2 mg/kg, 3-5 min before induction with ketamine IV, 2 mg/kg, given for 10 s.	No cardiovascular adverse event reporting methodology is presented. Respiratory status and Sao_2 were prospectively monitored and recorded. No psychiatric adverse event reporting methodology is presented.	No cardiovascular adverse events were reported. The mean preinduction Sao_2 was 96%. The Sao_2 nadir occurred at 3 min and was 55%. 30 patients had a saturation of 90% or less; of these 8 fell below 80% and received supplemental oxygen. Psychiatric adverse events were not reported.	Altitude 8500 ft, atmospheric pressure 570 mm Hg.
71 94	Sussman DR. A comparative evaluation of ketamine anesthesia	239 patients undergoing 247 assorted operations in a hospital in Guyana received IV ketamine,	Adverse event reporting methodology is not presented, however cardiorespiratory	In 86 patients 31 y or older, incidence of l aryngospasm was 4%, coughing 2%,	Dysphoria and patient acceptance not distinguished from emergence reactions.

		in children and adults. Anesthesiology 40:5, 459-64(1974) English.	2.2 mg/kg, or IM ketamine, 11 mg/kg, followed by supplemental smaller doses as needed with or without premedicant IM diazepam, 10-15 mg.	status seemed to be continuously monitored in the anesthesiologist-controlled operating room setting. The author reports that he saw all patients postoperatively and reviewed all nursing notes for complications.	upper airway obstruction 7%, inadequate analgesia 1%, excessive motor activity/hypertonus 16%, "dangerous" hyper-or hypotension 2%, and cardiac arrhythmia 1%. In patients 16 y old or older, emergence reactions occurred in 26% of patients who received diazepam and 22% of patients who did not receive diazepam.	
72	120	Swelem SE. Intravenous anaesthetics for minor gynecological operations. Middle East J Anaesthesiol 5:8, 545-51(1980) English.	118 patients undergoing minor gynecological procedures received either IV ketamine, 100 mg (n = 25), or IV diazepam, 10 mg, followed by IV ketamine (n = 93). An additional 352 patients received a variety of other anesthetic combinations in this study, including thiopental, althesin, propanidid, meperidine promethazine, hexobarbital, and buthalitone. Halothane supplementation was provided as needed, though none of the patients in either of the 2 ketamine groups required it.	Cardiorespiratory status was continuously monitored. Patients were monitored for "smoothness of recovery."	No cardiorespiratory adverse events occurred. 8% of patients in the ketamine-only group had "hallucinations" and 8% had an urticarial rash. Ketamine-diazepam was judged by the authors to be the "most satisfactory" of the 10 anesthetic combinations tested and judged superior to ketamine alone.	Dysphoria and patient acceptance not distinguished from postoperative hallucinations.
73	99	Taylor PA, Towey RM. Depression of laryngeal reflexes during ketamine anaesthesia. Br Med J 2:763, 688-9(1971) English.	7 patients received scopolamine, 0.4 mg, IM 1 hour before induction with ketamine, 2 mg/kg, which was maintained	Chest x-rays designed to detect the deposition of contrast in the lungs were taken 1, 2, and 5 min after contrast	The placement of contrast on the back of the tongue elicited a swallowing reflex in all 7 patients Partial	The clinical significance of the findings is unknown.

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Table 1 (*continued*)

A	B	C	D	E	F
		with a continuous infusion. 10 mL of contrast (Dionosil) was then placed on the back of the tongue. 7 controls received 0.4 mg IM of scopolamine and 1 h later swallowed 10 mL contrast.	ingestion. No other adverse event reporting methodology is presented.	laryngospasm developed in one control after given 2 mL contrast. There was no clinical indication of aspiration in any case, however, all 7 patients had evidence of contrast material present in the lungs on x-ray examination. This study was repeated 1 y later on 17 additional patients, who received either atropine or scopolamine as a premedicant. In the second study, 12 of 17 patients inhaled contrast.	
74 122	Tighe SQ, Rudland SV. Anesthesia in northern Iraq: an audit from a field hospital. Mil Med 159:2, 86-90(1994) eng.	Retrospective account of 71 anesthetic procedures carried out at a military field hospital in Sirsenk, Iraq. 12 patients were anesthetized using spontaneously breathing technique with IV ketamine, 1-2 mg/kg, and midazolam, 0.07 mg/kg.	No adverse event reporting methodology is presented.	"No patient receiving ketamine had unpleasant dreams or other sequelae."	Semiquantitative review; adverse events not specifically sought.
75 129	Tolksdorf, W, F Reinhard, M Hartung and S Bauman. Comparative study of the effects of midazolam-ketamine anesthesia and thiopental sodium induced enflurane-nitrous oxide anesthesia for minor gynecological operations,	60 patients undergoing minor gynecological operations received either thiopental, enflurane, and nitrous oxide (group 1, n = 30), IV midazolam 5 mg with IV ketamine, 0.5-1 mg/kg (group 2, n = 30), or IV midazolam, 7.5 mg,	Cardiorespiratory status was continuously monitored intraoperatively and postoperatively. "Psychiatric state" was prospectively assessed for 3 h postoperatively.	Two patients in group 2 received treatment of intraoperative hypertension. Assisted ventilation by BVM was performed for prespecified criteria and was needed in 40% of patients in	High midazolam dose.

		In Status of ketamine in anesthesiology, 481-90. Ann Arbor, Michigan: NPP Books, 1990.	with IV ketamine, 2-3 mg/kg (group 3, n = 30). Smaller supplementary doses were given as needed.		group 2 and 60% of patients in group 3. 1 patient in group 2 had unpleasant dreams; no unpleasant dreams occurred in group 3. Vomiting occurred in 8% of ketamine patients. Anesthesia was unacceptable in 2 patients in group 2. The remainder of patients in groups 2 and 3 had "positive" or "moderate" acceptance of the anesthetic.	
76	112	Trouwborst A, Weber BK, Dufour D. Medical statistics of battlefield casualties. Injury 18:2, 96-9(1987) eng.	Retrospective account of 1033 anesthetic procedures carried out at 2 military field hospitals near the Thailand/Cambodia border. 516 patients were anesthetized using spontaneously breathing technique with IV ketamine, 2 mg/kg, and either diazepam, 0.2 mg/kg, or midazolam, 0.1 mg/kg.	No adverse event reporting methodology is presented.	No adverse events are attributed to ketamine; however, no mention of ketamine's safety is found in the article.	Semiquantitative review; adverse events not specifically sought.
77	133	Veeken H. Ketamine drip anaesthesia for caesarean section. Trop Doct 19:1, 47(1989) eng.	Brief historical account of 40 patient undergoing cesarean delivery in a Kenyan hospital. In all patients the skin was opened under local anesthesia, without any systemic agents or premedicants. Just before uterine incision, IV ketamine, 75 mg, was administered as a one-time bolus.	No adverse event r eporting methodology is presented.	"No complications" occurred in this cohort. No further details are given.	Descriptive review.

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Table 1 (*continued*)

	A	B	C	D	E	F
78	125	Vinnik CA. An intravenous dissociation technique for outpatient plastic surgery: tranquility in the office surgical facility. Plast Reconstr Surg 67:6, 799-805(1981) eng.	Historical account of >2000 patients undergoing plastic surgery procedures (breast augmentation, facial fracture reductions, and blepharoplasty, among others) performed in an office setting, without an anesthesia MD or RN. For procedures expected to be of >2 hour duration, patients were premedicated with PO lorazepam, 4 mg; IM butorphanol, 0.4 mg; and IM promazine, 25 mg, 1 h before surgery. For shorter procedures, no premedicants were used. All patients received IV diazepam, 5 mg, followed several minutes later by 10 mg increments until responsive only to painful stimuli (usual dose, 25 mg). Afterward, all patients received IV ketamine, 75 mg, with additional 25-50 mg doses of ketamine and 10 mg doses of diazepam as needed for the duration of surgery. In addition, a survey of 100 randomly selected patients receiving this technique within 6 y was carried out by an affiliated RN.	Blood pressure, pulse rate, and electrocardiogram tracing were continuously monitored. No psychiatric adverse event reporting methodology is presented in the historical account; the structured survey was designed to retrospectively assess psychological adverse events.	The author reports the absence of any cardiorespiratory or psychiatric adverse events in this series. 94% of survey respondents reported absence of any recollection of the surgery. All respondents denied postoperative delirium, hallucinations, or “bad trips,” and all respondents would recommend the anesthetic technique. Four years later, this author published an additional account of several thousand more patients, further attesting to the safety and efficacy of the technique.	The case series is a descriptive review, and the survey results are subject to all the limitations of this design.
79	107	Weerasekera DS, Gunawardene KK. Ketamine as an	Retrospective observational study of 4851 patients	A theater nurse was assigned to monitor cardiorespiratory status	No cardiorespiratory complications occurred in this cohort.	Retrospective study. Dysphoria and patient acceptance not

		anaesthetic agent for tubal sterilisation. Ceylon Med J 41:3, 102-3(1996) English.	undergoing tubal ligation in a Sri Lankan hospital. All patients received IV diazepam, 0.1 mg/kg, followed by IV ketamine, 2 mg/kg, given for 1 min.	throughout the procedure. No psychiatric adverse event reporting methodology is presented.	"Postoperative hallucinations within the first 6 h after surgery was observed in most patients." 96% of patients had no recollection of the surgery when questioned at 24 h.	distinguished from postoperative hallucinations.
80	95	White PF, Ham J, Way WL, Trevor AJ. Pharmacology of ketamine isomers in surgical patients. Anesthesiology 52:3, 231-9(1980) eng.	60 patients undergoing dilation and curettage were randomized to receive racemic ketamine, (+)ketamine, or (−)ketamine. Patients received racemic ketamine, 2 mg/kg, or its isomeric equivalent in double-blind fashion.	Cardiorespiratory adverse events were prospectively sought. Psychiatric adverse events were prospectively sought postoperatively by a trained psychologist according to a standardized protocol.	No adverse cardiorespiratory events occurred in any group. In the 20 patients in the racemic group, the incidence of adverse psychiatric events ranged between 10% and 30%, depending on the measurement used, and ketamine acceptability was 65%. Of note, the positive enantiomer was superior to the racemic mixture at almost all measured end points, whereas the converse was true for the negative enantiomer.	
81	28	Willman EV, Andolfatto G. A Prospective Evaluation of "Ketofol" (ketamine/ propofol Combination) for Procedural Sedation and Analgesia in the Emergency Department. Ann Emerg Med 49:23-30(2007) ENG.	114 patients undergoing a variety of ED procedures received a 1:1 mixture of ketamine (10 mg/mL) and propofol (10 mg/mL) delivered in 1-3 mL aliquots. Some patients received opioid analgesics preprocedure.	Cardiorespiratory and psychiatric adverse events were prospectively recorded on a standardized form.	No cardiovascular adverse events occurred. 3 patients had oxygen desaturation, with one patient requiring BVM ventilation. 3 patients required airway repositioning. 1 patient developed an agitation on emergence requiring IV midazolam, 0.025 mg/kg. 2 patients had "mild dysphoria" requiring no intervention.	No control group.

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Table 1 (*continued*)

A	B	C	D	E	F
				No postprocedure vomiting occurred. Median ketofol dose was 0.75 mg/kg of propofol and ketamine. 96.5% procedures required no additional medication. Median satisfaction scores (rated from 0 to 10) were 10, 10, and 10 for physicians, nurses, and patients.	
82 132	Zimmermann H. Ketamine drip anaesthesia for caesarean section. Report on 200 cases from a rural hospital in Zimbabwe. Trop Doct 18:2, 60-1(1988) English.	200 patients undergoing cesarean delivery at rural Zimbabwean hospital received IV ketamine, 100 mg, given for 60 s,followed by a maintenance drip. Diazepam or flunitrazepam were given intravenously as needed postoperatively "to provide a sound sleep and depress possible psychomimetic reactions." Most cases were managed by nonphysician "auxillaries."	No adverse event reporting methodology is presented.	5 cases required a change in anesthesia with oxygen, nitrous oxide, and halothane for surgical extension of the procedure. In the 195 remaining cases, no cardiorespiratory adverse events occurred. Psychiatric adverse events were not quantified, but diazepam was given postoperatively in 15.5% of patients and flunitrazepam in 9.5%. Note patients in this series of cesarean deliveries were unfasted.	It is unclear if data were collected prospectively or reviewed retrospectively in this study. Relationship between decision to treat and patient dysphoria/ acceptance unknown.
83 119	Zohairy AF, Siddiqi SM. The use of ketamine HCl in minor surgery. Middle East J Anaesthesiol 3:121-9(1971)	237 patients undergoing minor surgical procedures in a Qatar hospital were studied. All adults (74% of patients) received IV meperidine, 50 mg, and IV phenergan, 25 mg, 45 min before induction with IV ketamine, 2 mg/kg, followed by smaller doses as needed. Most children received IM ketamine, 4 mg/kg.	Cardiorespiratory status was continuously monitored. No psychiatric adverse event reporting methodology is presented but "trained nurses" observed patients for postoperative complications.	No cardiorespiratory adverse events occurred. An erythematous rash about the neck and upper chest occurred in 8% of patients and resolved within 15 min. 2% of patients had "emergence delirium with excitation" and were "easily managed" with meperidine. Postoperative emesis occurred in 4% of patients.	Dysphoria and patient acceptance not distinguished from emergence delirium.

84	87	Zsigmond EK, Matsuki A, Kothary SP, Jallad M. Arterial hypoxemia caused by intravenous ketamine. Anesth Analg 55:3, 311-4(1976) English.	14 patients undergoing gynecologic surgery were premedicated with IM diazepam, 0.15 mg/kg, and either meperidine, 1.5 mg/kg, or morphine, 0.15 mg/kg. 7 patients were then induced with IV ketamine, 2 mg/kg, given for 30 s, and 7 patients were induced with IV diazepam, 0.2 mg/kg, given for 30 s followed 5 min later by ketamine, 2 mg/kg, given for 30 s. Arterial blood gas samples were obtained at time 0, 2, 5, and 10 min after ketamine administration. The study design stipulated that no airway-opening maneuvers were performed.	In addition to serial blood gas measurements, electrocardiogram, pulse, and blood pressure were continuously monitored throughout the study. Chest movements were monitored by plethysmography. No psychiatric adverse event reporting methodology is presented.	The time of greatest respiratory depression occurred 2 min postinjection. At that time, mean Pao_2 values decreased from baseline 84-58 Torr, with $PaCO_2$ values rising from baseline 34- 38 Torr. Mean arterial pH at 2 min postinjection was 7.37. Respiratory rate decreased from baseline 19 breaths per minute to 11 at 2 min. More than half of the patients had brief periods of apnea. The ketamine/diazepam group did not show any significant difference when compared to the ketamine group. Blood pressure and heart rate were both elevated after ketamine administration; this effect was significantly attenuated by concurrent diazepam administration.	Two respiratory depressants given to all patients.
85	137	Klose R, Peter K. Clinical studies on single-drug anesthesia using ketamine in patients with burns. Anaesthesist 22:3, 121-6(1973) German.	41 adult patients undergoing burn-related p rocedures at a German specialty burn clinic received IV ketamine, 4-5 mg/kg, followed by 1-2 mg/kg doses as needed.	No adverse event reporting methodology is presented.	2 episodes of hypotension are reported, as well as 1 episode of cyanosis. "Motor agitation" occurred in 3 patients intraoperatively and 6 patients postoperatively. One patient had “dreams” postoperatively.	Unclear methodology. Much larger ketamine dose than is currently recommended.
86	138	Vidal Cerdán J. Comments on 400 anesthesias with ketamine	A historical description of 400 patients undergoing unspecified types of operations or painful	No adverse event reporting methodology is presented.	Blood pressure noted to increase an average of 10 mm Hg without any elevations requiring	Descriptive review.

(continued on next page)

Table 1 (*continued*)

A	B	C	D	E	F
	chlorhydrate. Rev Esp Anestesiol Reanim 18:2, 244-59(1971) Spanish.	transport at a Spanish center. 133 patients received IV ketamine alone at a dose of 1-3.5 mg/kg; others received barbiturate and/or narcotic pretreatment.		treatment. 2 patients required airway repositioning. One patient required intubation. Psychiatric adverse effects were observed but not quantified.	
87 140	Mauad Filho F, Meirelles RS. [Materno-fetal acid-base equilibrium evaluation in (author's transl)]. Rev Bras Pesqui Med Biol 8:5-6, 401-13(1975) Portuguese.	22 patients in labor were given IV ketamine, 1 mg/kg, with supplemental doses of 0.5 mg/kg as needed. These patients were compared with 20 control patients in labor who received no medications. A variety of maternal and fetal physiologic parameters were prospectively studied.	Basic maternal and fetal vital signs appear to have been prospectively measured. Psychiatric adverse event methodology is not reported.	Control group results are not reported. 1/22 experimental patient experienced apnea, 1 nausea, 4 "perineal rigidity," 4 "dreams/ hallucinations." 11/22 patients demonstrated a significant increase in blood pressure.	Results are poorly reported. Dysphoria and patient acceptance not distinguished from dreams/hallucinations.
88 139	Tarnow J, Hess W. Pulmonary hypertension and pulmonary edema caused by intravenous ketamine. Anaesthesist 27:10, 486-7(1978) German.	Case report of a patient with coronary artery disease who developed acute pulmonary edema after receiving IV ketamine, 1.5 mg/kg, for induction of anesthesia.	No adverse event reporting methodology is presented. Patient was in a setting where advanced monitoring, including pulmonary artery catheter measurements, was performed.	After ketamine administration, mean pulmonary artery pressure rose from 27-65 mm Hg, pulmonary vascular resistance increased threefold and left ventricle filling pressure increased from 18-48 mm Hg. These hemodynamic derangements were associated with pulmonary edema and resultant arterial hypoxemia. Fentanyl .01 mg/kg "promptly reversed the systemic and pulmonary vascular effects of ketamine."	Case report methodology.

Because no such agent exists, the emergency practitioner must choose the drug or drug combination best suited to the goals of the procedure and the characteristics of the patient and practice environment.

Fentanyl and midazolam offer the weight of tradition but are consistently associated with the highest complication rate among modern procedural sedation regimens [23,147-149]. Although providing analgesia, amnesia, anxiolysis and reversibility, this combination has a comparatively delayed peak effect and prolonged duration of action with a narrow therapeutic index, which hinders effective titration [150]. Propofol features favorable pharmacokinetics but no analgesia; painful procedures therefore require aggressive dosing to bring about comparatively deeper sedation, which exposes the patient to its potent vasodilatory and respiratory depressant properties that may become clinically significant in longer procedures [151-155]. Propofol's fleeting duration of action does reduce the risk of adverse events [156,157], and propofol produces a high degree of muscle relaxation which is advantageous in orthopedic reductions [158]. Etomidate is rapidly metabolized and provides unmatched hemodynamic neutrality but also lacks analgesic efficacy and may cause respiratory depression [150,159,160]. Its use in procedural sedation is complicated by a relatively high incidence of vomiting and disruptive myoclonus [159,161-165].

Ketamine effectively provides anesthesia for procedural sedation and protects patient safety. It is alone in its predictable effect when administered by the intramuscular route, with peak levels occurring in 4 to 6 minutes and when given intravenously causes dissociation within 1 to 2 minutes. Its duration of action is 20 to 40 minutes intramuscularly and 10 to 15 minutes intravenously, an advantage when compared to fentanyl/midazolam [48,166]. Although recovery time is longer than with propofol or etomidate, ketamine offers analgesia that outlasts sedation —a benefit in the patient who is expected to have postprocedure pain [126]. Ketamine has a number of unique adverse effects, however, that must be anticipated by providers.

Airway and breathing are rarely compromised when ketamine is used as monotherapy. Every day thousands of patients undergo operations facilitated by ketamine in comparatively spartan settings with minimal monitoring at the hands of a single operator who performs the procedure and the anesthesia [53,134]. That so few adverse events result from this practice attests to ketamine's cardiorespiratory dependability; however, the potential for respiratory depression and airway malpositioning is well documented. As apnea appears to be more likely with large intravenous bolus doses administered rapidly, ketamine should be dosed according to ideal body weight and infused for 1 to 2 minutes.

Continuous hemodynamic monitoring including pulse oximetry is the standard of care for procedural sedation where such equipment is available. The emergency physician must be mindful that comedications, particularly midazolam, may cause dose-related hypoventilation, and in all procedural sedation cases should be prepared to provide airway and respiratory support.

Ketamine causes centrally mediated catecholamine reuptake inhibition that generally results in a modest increase in heart rate and an elevation of blood pressure, which on occasion can be marked. This is not a concern in most ED patients and there are no reports of ketamine-induced myocardial ischemia. Furthermore, the literature is replete with studies of ketamine use in the elderly [60,63,72,89], including its use in coronary artery bypass grafting, where it continues to be favored by some cardiothoracic surgeons [53]. However, whereas the stimulation of cardiac output is an advantage in the hypotensive patient, the resulting increase in myocardial oxygen demand can be consequential [167], and in patients known for or at risk for coronary artery disease, caution is prudent. Ketamine's cardiostimulatory effect is blunted by pharmacologic sympatholysis; drugs in the benzodiazepine, opioid, and β-adrenergic antagonist class have been proven effective in this regard. A practical approach is to carefully monitor rate-pressure product in patients with risk factors and, in the event of a concerning rise, give small doses of midazolam or fentanyl to effect. The patient with known severe atherosclerotic heart disease may not be an appropriate candidate for ketamine or any procedural sedation, depending on the urgency of the procedure.

The use of ketamine for procedural sedation is most likely to be complicated by psychological emergence reactions. Most unpremedicated patients experience dreams or hallucinations that may be perceived as odd or enjoyable; indeed ketamine is used recreationally for this purpose. As patients reintegrate external stimuli, 10% to 20% of patients, however, go through frightening depersonalization. Although not dangerous, such experiences can be associated with considerable distress. They are readily managed with benzodiazepines, and their occurrence can be reduced with environmental techniques such as the provision of music or a quiet recovery area. Although this may not be feasible in emergency settings, patients can be coached preinduction to great effect. We find explaining the likelihood of dreaming, and offering to the patient that they may choose their dream, if desired, requires little time and produces satisfying results.

Several pharmacological approaches to ketamine's potential to cause psychiatric adverse effects are acceptable.

Predissociation strategy. Administration of a sedative (most often a benzodiazepine, but propofol shows promise in this role [28]) before or with ketamine reliably reduces the incidence of emergence reactions, in some cases to zero [61,70,97]. Respiratory depression is increased and recovery prolonged in a dose-dependent manner. In a study by Chudnofsky et al [27], 70 ED patients received intravenous midazolam, 0.07 mg/kg, a relatively high dose, which led to 99% patient satisfaction but produced 3 instances of respiratory depression, 2 of which required BVM ventilation.

Preemergence strategy. Adverse psychiatric events occur in the recovery period, therefore the administration of a sedative shortly before emergence results in their abolition with efficacy equal to a predissociation strategy [108]. The advantage of this approach is that the peak effect of the sedative corresponds to the vulnerable period in the patient's recovery, so a smaller sedative dose can be used. However, most procedural sedation adverse events occur in first minutes after drug administration [147], and if a sedative is to be given routinely, it may be preferable for its peak effect to occur when multiple providers are at the bedside.

PRN strategy. This is the approach of choice in the pediatric population, where prophylactic sedation confers no benefit [13,168]. It is a sensible option in adults, who are more prone to adverse psychiatric events, as long as it is combined with preinduction counseling and attentive surveillance for signs of psychiatric discomfort, which should be managed with prompt administration of a potent, titratable sedative (eg, midazolam). This strategy minimizes the risk of respiratory depression and will shorten the time to recovery in most patients who will not require sedative cotherapy.

Regardless of the strategy chosen, the provider must be vigilant in recognizing and treating emergence reactions at their first appearance, as the transition to conscious perception can be terrifying [169].

The development of a severe emergence reaction is a traumatic experience for an entire ED. Still, the possibility of such an event should not drive decisions to use ketamine for procedural sedation on adult patients, as proficient application will preclude their occurrence. Furthermore, providers who dismiss ketamine for procedural sedation may overlook it in situations of greater urgency, where its unique pharmacology may be of particular benefit and psychiatric adverse effects are of little concern. Such situations include therapy for severe asthma [170], RSI in hemodynamically tenuous conditions and management of the uncontrollably violent patient [117].

Finally, studies unambiguously indicate that (S)+ketamine, or *esketamine,* offers higher potency, shorter duration of action, and fewer adverse effects—including a marked reduction in emergence reactions—compared to the racemic mixture [50,171-174]. The isomeric preparation is available in Europe and deserves further study in the ED setting.

6. Limitations

Literature reviews are nonexperimental and do not produce new data. Their purpose is to group existing data with the expectation that the weight of the aggregate will provide more explanatory power than the component studies provide individually. *A quantitative* systematic review, also known as a meta-analysis, pools data from disparate studies using statistical methods to generate a larger dataset [175]. The strength of a meta-analysis corresponds to both the strength of its component studies and on the ability of a reviewer to combine the results of the component studies, which in turn is dependent on the similarity of their methods [176]. In the present review, we sought to collect all studies pertinent to emergency medicine practice. These articles range from surveys of developing-world physicians to case reports to sophisticated blinded experiments in tightly controlled operating room settings. Patient populations, provider characteristics, dosing, and comedication regimens were far too varied for quantitative combination. We therefore performed a *narrative review,* which presents a complete survey of the literature with results not numerically pooled but reported as structured abstracts with a holistic analysis [175]. This type of methodology is subject to a variety of weaknesses [32,177]; however, given ketamine's low adverse event rate, a prospective trial of sufficient size to assess safety is unlikely to be performed, and we felt a qualitative review offered the best means to answer our research question.

In attempting to select studies relevant to procedural sedation in the ED from thousands of articles published primarily in the anesthesia literature, we defined a set of exclusion criteria that are imperfect both in their efficacy and in their application. For example, we excluded studies on intubated patients and studies that used continuous cotherapies to supplement ketamine anesthesia. Although the presence of an endotracheal tube precludes airway and breathing adverse event reporting, this criterion also excludes valid data on emergence reactions; furthermore, some studies do not indicate whether patients were intubated for the procedure. Reviewing articles from decades past presented additional obstacles in applying exclusion criteria, as many abstracts are not available in their referring databases and methods sections are of inconsistent quality.

Lastly, although we formulated strict adverse event definitions *a priori,* our efforts to systematically account for such events were confounded by the nebulous nature of an adverse event itself. A clinically significant adverse event occurs when the patient has obvious harm, or the provider must perform an important therapeutic maneuver but what counts as important is difficult to define. For example, most procedural sedation literature considers BVM ventilation an important therapeutic maneuver, but it is unclear how many episodes of respiratory depression treated with BVM ventilation would have resolved uneventfully without intervention. One study of 8000 patients in a tropical single-provider environment reported minimal adverse events [134] while in an anesthesiologist-controlled modern operating room; of 76 patients who were given a similar medication regimen, 2 required endotracheal intubation for apnea [105]. This provocative discrepancy may be because of underreporting of adverse events in the larger study, but another explanation is that the incidence of reported adverse events depends not only on patient or drug characteristics

but on how assiduously such events were sought and how much deviation from normal physiology was tolerated before an intervention performed. Because the therapeutic maneuvers themselves are associated with risk, it is possible that when administering a very safe drug, more advanced monitoring techniques might actually cause more harm than they prevent.

7. Conclusion

When ketamine is used for procedural sedation in adults, emergence phenomena occur in 10% to 20% of unpremedicated and uncoached patients. Although providers must be prepared to recognize and manage airway obstruction, cardiorespiratory adverse events are rare and typically do not affect outcomes.

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